Chemistry

SALICYLALDEHYDES DERIVED FROM 5-CHLOROMETHYL-2-HYDROXYBENZALDEHYDE − SYNTHESIS AND REACTIONS

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Abstract. A series of salicylaldehydes have been prepared through the replacement of the easily leaving chlorine atom in 5-chloromethyl-2-hydroxybenzaldehyde with various *O*-, *S*- or *N*-nucleophiles. The involvement of a few of these salicylaldehydes in the synthesis of heterocycles such as benzofuran or coumarin, or as substrate in the Petasis borono-Mannich reaction has been explored.

Keywords: 2-hydroxybenzaldehydes, nucleophilic substitution, NMR analysis, heterocyclic synthesis, Petasis reaction.

1. Introduction

Salicylaldehyde and analogous *ortho*-hydroxybenzaldehydes substituted in the aromatic ring with various functional groups represent valuable starting materials for the synthesis of oxygen-containing heterocycles owing to the favorable arrangement of the adjacent hydroxyl and carbonyl groups in their structure. For example, salicyladehydes lead to a variety of structures that have in common a chromane scaffold upon reaction with enolates or their structural equivalents.[1] Alkene- or alkyne-tethered salicylaldehyde derivatives (such as *O*-allylsalicylaldehyde or *O*-propargylsalicylaldehyde) can generate diverse compound libraries with rich stereochemical and scaffold diversity that include benzopyranes, chromenoquinolines, various other chromene-fused heterocycles, benzoxazepines and macrocycles.[2,3] Upon cyclocondensation with α-haloketones under the conditions of the Rap–Stoermer reaction, salicylaldehydes produce 2-acylbenzofurans,[4,5] while this particular reaction was shown to be amenable to an ultrasound-assisted approach that improves the yields of the target benzofurans.[6] Also, several synthetic variants for the preparation of 1,2-benzisoxazoles from oximes of *ortho*-hydroxybenzaldehydes using *para*-toluenesulfonyl chloride in the presence of an amine in acetonitrile,[7] trifluoromethanesulfonic anhydride in dichloromethane,[8] or a triphenylphosphine–

2,3-dichloro-5,6-dicyano-1,4-benzoquinone system[9] have been reported. In addition, examples of salicyaldehydes as starting materials in multicomponent reactions[10] or in domino reactions[11] are available. In this context, it is worth mentioning the role of salicylaldehydes as one of the preferred substrates in the multicomponent Petasis borono-Mannich reaction that leads to a wide structural range of functionalized amines.[12,13] Last but not least, salicylaldehydes and their derivatives (*e.g.*, oximes, imines, semicarbazones, hydrazones, *etc*.) are well known for their ability to form complexes with metal ions.[14–16] Such complexes have been useful as catalysts for the oxidative coupling of phenols,[17] optical chemical sensors,[18] fluorescent chemosensors,[19,20] or anticancer agents.[21]

The majority of the reactions in which salicylaldehydes are employed as starting materials have been performed mostly with the narrow, yet significant number of commercially available *ortho*-hydroxybenzaldehydes. However, the broadening of the range of usable salicylaldehydes in these applications could be accomplished either through one of the known synthetic methodologies for the formylation of phenols (Gattermann, Reimer–Tiemann, Vilsmeier–Haack, Rieche or Duff reactions), or through the electrophilic substitution of a commercial salicylaldehyde. As an example of the latter approach, Blanc chloromethylation of *ortho*-hydroxybenzaldehydes and subsequent nucleophilic replacement of the easily leaving chlorine anion in the chloromethyl-substituted intermediate have been scantily reported as a synthetic strategy for the generation of a limited number of novel and otherwise difficult to obtain salicylaldehydes with interesting structures.[22,23] The present study exploits this strategy for the preparation of several 5-substituted salicylaldehydes, and briefly explores their potential for the generation of heterocycles and aminobenzylated phenols.

2. Experimental

2.1. Materials and Methods

All reagents and solvents were purchased from commercial suppliers (Sigma–Aldrich, TCI Europe N.V., Merck KGaA) and were used without further purification.

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Melting points were taken on a Mel Temp II apparatus and are uncorrected. Analytical thin layer chromatography was carried out on glass-backed precoated plates (Merck silica gel 60, F254) and visualized with UV light. Flash column chromatography was performed on Merck silica gel (230–400 mesh). NMR spectra were recorded on a Bruker Avance NEO spectrometer operating at 400 MHz, with a 5 mm probe for direct detection of ^{1}H, ^{13}C, ^{19}F, and ^{29}Si. The spectra were recorded at room temperature using the standard parameter sets provided by Bruker. The residual signals of the deuterated solvents were used as internal standard (DMSO-d_6: $\delta = 2.51$ ppm for ^{1}H and $\delta = 39.5$ ppm for ^{13}C; CDCl$_3$: $\delta = 7.26$ ppm for ^{1}H and $\delta = 77.0$ ppm for ^{13}C). Elemental analysis was performed on a Vario EL III CHNS instrument. 1-Benzylbenzimidazole was obtained through the *N*-alkylation of benzimidazole with benzyl chloride using one of the procedures reported in the literature.[24]

2.2. Synthesis

Blanc chloromethylation of salicylaldehyde 1

A mixture of salicylaldehyde **1** (2.44 g, 20 mmol), paraformaldehyde (600 mg, 20 mmol), and aqueous 36.5% HCl (20 mL) was vigorously stirred at room temperature for 24 h. The solid that formed was filtered, washed thoroughly with water, and then dissolved freely in chloroform (10–15 mL). The mixture was dried over anhydrous Na$_2$SO$_4$, the drying agent was filtered, and the solvent in the filtrate was removed under reduced pressure. The pinkish material was then dissolved in hot hexanes (approximately 50 mL), and the solution was filtered while hot. A colorless solid formed upon cooling, and after being refrigerated overnight, the crystals were filtered, washed with fresh hexanes (2 × 10 mL), and air-dried. Yields ranged from 48% to 38% for different batches. The obtained 5-(chloromethyl)-2-hydroxybenzaldehyde **2** had m.p. 84–85 °C, which is close to the literature one (Kadwa *et al.* reported[25] a melting point of 84–86 °C). ^{1}H NMR (CDCl$_3$, 400 MHz), δ (ppm): 4.59 (s, 2H), 7.00 (d, *J* = 8.8 Hz, 1H), 7.56 (dd, *J* = 2.4 and 8.4 Hz, 1H), 7.59 (d, *J* = 2.0 Hz, 1H), 9.90 (s, 1H), 11.07 (s, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz), δ (ppm): 45.4, 118.5, 120.5, 129.4, 133.8, 137.4, 151.7, 196.3. *Anal.* calcd. for C$_8$H$_7$ClO$_2$, %: C, 56.32; H, 4.14; Cl, 20.78. Found, %: C, 56.59; H, 3.97; Cl, 20.42.

Reaction of 5-(chloromethyl)-2-hydroxybenzaldehyde 2 with methanol

Finely ground NaHCO$_3$ (336 mg, 4 mmol) was added to a solution of 5-(chloromethyl)-2-hydroxybenzaldehyde **2** (341 mg, 2 mmol) in methanol (10 mL), and the resulting suspension was stirred at room temperature for 4 h, then the flask was placed in an oil bath heated at

50°C, and was further stirred for 4 h. The solvent was removed under reduced pressure, and the residue was partitioned between diethyl ether (10 mL) and water (10 mL). The organic phase was further washed with water (2 × 10 mL), and then was dried over anhydrous Na$_2$SO$_4$. Gravity filtration afforded a yellowish solution, from which the solvent was removed under reduced pressure to give a dense oil consisting of a mixture of 2-hydroxy-5-(methoxymethyl)benzaldehyde **3** and its dimethyl acetal. The oily material was dissolved in acetone (10 mL), 3 drops of water and Amberjet 1200(H) (50 mg) were added, and the mixture was stirred at room temperature for 5 h. Filtration of the catalyst and removal of acetone under reduced pressure afforded aldehyde **3** as a yellow oil (163 mg, 49%) which was pure according to NMR. ^{1}H NMR (CDCl$_3$, 400 MHz), δ (ppm): 3.40 (s, 3H), 4.42 (s, 2H), 6.98 (d, *J* = 8.4 Hz, 1H), 7.49 (dd, *J* = 2.0 and 8.4 Hz, 1H), 7.54 (d, *J* = 2.0 Hz, 1H), 9.89 (s, 1H), 10.99 (s, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz), δ (ppm): 58.3, 73.7, 117.9, 120.5, 130.0, 133.0, 136.8, 161.3, 196.7. *Anal.* calcd. for C$_9$H$_{10}$O$_3$, %: C, 65.05; H, 6.07. Found, %: C, 64.70; H, 5.72.

Preparation of 2-hydroxy-5-(isopropoxymethyl)benzaldehyde 4

A mixture of 5-(chloromethyl)-2-hydroxybenzaldehyde **2** (682 mg, 4 mmol) and finely ground NaHCO$_3$ (672 mg, 8 mmol) in 2-propanol (10 mL) was stirred at room temperature overnight (18 h), and then the mixture was heated (oil bath temperature 50°C) for 4 h. The suspension was allowed to reach room temperature, and then the inorganics were filtered and washed with fresh 2-propanol (10 mL) to give a filtrate from which the solvent was removed under reduced pressure. The resulting yellow oil (745 mg, 96%) consisted of the desired product **4** with 95% purity according to NMR. The analytical sample (*R*$_f$ 0.27, dichloromethane) was obtained after column chromatography using dichloromethane as mobile phase. ^{1}H NMR (CDCl$_3$, 400 MHz), δ (ppm): 1.23 (d, *J* = 6.0 Hz, 6H), 3.70 (sept., 1H), 4.47 (s, 2H), 6.96 (d, *J* = 8.4 Hz, 1H), 7.50 (dd, *J* = 2.0 and 8.4 Hz, 1H), 7.55 (d, *J* = 2.0 Hz, 1H), 9.89 (s, 1H), 10.98 (s, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz), δ (ppm): 22.1, 69.0, 71.3, 117.7, 120.3, 130.7, 132.6, 136.6, 161.0, 196.6. *Anal.* calcd. for C$_{11}$H$_{14}$O$_3$, %: C, 68.02; H, 7.27. Found, %: C, 67.66; H, 6.94.

Synthesis of 2-hydroxy-5-(morpholinomethyl)benzaldehyde 5

To a solution of 5-(chloromethyl)-2-hydroxybenzaldehyde **2** (1023 mg, 6 mmol) in acetone (10 mL), anhydrous K$_2$CO$_3$ (2.48 g, 12 mmol) was first added, followed by a solution of morpholine (522 mg, 6 mmol) in

acetone (5 mL). The yellow suspension was vigorously stirred at room temperature overnight (18 h), then the inorganics were filtered and washed with acetone (2×10 mL). The solvent in the filtrate was removed under reduced pressure, and then the residue was partitioned between diethyl ether (20 mL) and water (30 mL). The organic phase was washed with water (2×15 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to afford an oil which crystallized slowly upon cooling to a reddish mass of crystals (756 mg, 57%) consisting of aldehyde **5** with m.p. 90–91°C (lit.[26] m.p. 92–93°C). ^{1}H NMR (DMSO-d_6, 400 MHz), δ (ppm): 2.32 (t, $J = 4.4$ Hz, 4H), 3.39 (s, 2H), 3.55 (t, $J = 4.4$ Hz, 4H), 6.96 (d, $J = 8.4$ Hz, 1H), 7.45 (dd, $J = 2.0$ and 8.4 Hz, 1H), 7.55 (d, $J = 2.0$ Hz, 1H), 10.25 (s, 1H), 10.65 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz), δ (ppm): 53.0, 61.4, 66.2, 117.2, 121.9, 128.8, 129.2, 137.2, 159.9, 191.6. *Anal.* calcd. for $C_{12}H_{15}NO_3$, %: C, 65.14; H, 6.83; N, 6.33. Found, %: C, 65.28; H, 6.51; N, 6.04.

Reaction of 5-(chloromethyl)-2-hydroxybenzaldehyde 2 with 4-chlorothiophenol

A solution of 5-(chloromethyl)-2-hydroxybenzaldehyde **2** (682 g, 4 mmol) and 4-chlorothiophenol (578 mg, 4 mmol) in chloroform (15 mL) was treated with $NaHCO_3$ (672 mg, 8 mmol), then the suspension was efficiently stirred at room temperature overnight (18 h). The solid material was removed by filtration and washed with fresh chloroform (2×10 mL), and then the solvent was removed from the filtrate under reduced pressure to give a colorless oil which crystalized upon cooling. The solid is recrystallized from isopropanol (10 mL) to afford colorless crystals of 5-{[(4-chlorophenyl)thio]methyl}-2-hydroxybenzaldehyde **6** (645 mg, 58%), m.p. 76–77°C (lit.[27] m.p. 82°C). ^{1}H NMR (CDCl$_3$, 400 MHz), δ (ppm): 4.05 (s, 2H), 6.93 (d, $J = 8.4$ Hz, 1H), 7.18–7.26 (m, 4H), 7.38–7.42 (m, 1H), 7.43 (d, $J = 2.4$ Hz, 1H), 9.82 (s, 1H), 10.96 (s, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz), δ (ppm): 38.6, 118.0, 120.3, 128.8, 129.1, 132.0, 133.1, 133.5, 133.8, 137.5, 160.9, 196.3. *Anal.* calcd. for $C_{14}H_{11}ClO_2S$, %: C, 60.32; H, 3.98; Cl, 12.72; S, 11.50. Found, %: C, 60.60; H, 4.12; Cl, 12.98; S, 11.18.

Preparation of 2-hydroxy-5-(thiocyanatomethyl)benzaldehyde 7

A solution of KSCN (300 mg, 3 mmol) in acetone (5 mL) was added to a solution of 5-(chloromethyl)-2-hydroxybenzaldehyde **2** (511.5 g, 3 mmol) in acetone (5 mL), and then the mixture was stirred at room temperature overnight (18 h). Gradual dilution of the reaction mixture with water up to 50 mL afforded an emulsion which turned into a solid material over the weekend. The

solid was filtered, air-dried and extracted with a hot mixture of isopropanol and hexanes (50 mL, 1:4 v/v). After a small amount of insoluble material was removed by filtration of the hot solution, the filtrate was refrigerated overnight to afford a solid material from which a second recrystallization from a mixture of 2-propanol–hexanes (1:4 v/v) provided aldehyde **7** as colorless plates (250 mg, 43%), m.p. 59–60°C. ^{1}H NMR (CDCl$_3$, 400 MHz), δ (ppm): 4.16 (s, 2H), 7.04 (d, $J = 8.8$ Hz, 1H), 7.54 (dd, $J = 2.4$ and 8.8 Hz, 1H), 7.58 (d, $J = 2.0$ Hz, 1H), 9.91 (s, 1H), 11.11 (s, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz), δ (ppm): 37.5, 111.5, 118.9, 120.5, 126.0, 134.0, 137.4, 162.0, 196.0. *Anal.* calcd. for $C_9H_7NO_2S$, %: C, 55.94; H, 3.65; N, 7.25; S, 16.59. Found, %: C, 56.13; H, 3.81; N, 7.03; S, 16.26.

N-Alkylation of 1-benzyl-1H-imidazole with 5-(chloromethyl)-2-hydroxybenzaldehyde 2

A mixture of 5-(chloromethyl)-2-hydroxybenzaldehyde **2** (511.5 mg, 3 mmol)) and 1-benzyl-1*H*-imidazole (474 mg, 3 mmol) in toluene (15 mL) was stirred under heating (oil bath temperature 70°C) for 24 h. The solid was filtered, washed with diethyl ether (2×10 mL), air-dried and recrystallized from absolute ethanol (10 mL) to afford 1-benzyl-3-(3-formyl-4-hydroxybenzyl)-1*H*-imidazol-3-ium chloride **8** as colorless crystals (595 mg, 60%), m.p. 212–214°C. ^{1}H NMR (DMSO-d_6, 400 MHz), δ (ppm): 5.37 (s, 2H), 5.43 (s, 2H), 7.12 (d, $J = 8.8$ Hz, 1H), 7.37–7.48 (m, 5H), 7.62 (dd, $J = 2.4$ and 8.8 Hz, 1H), 7.63 (d, $J = 2.4$ Hz, 1H), 7.80–7.86 (m, 2H), 9.42 (s, 1H), 10.31 (s, 1H), 11.12 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz), δ (ppm): 51.3, 52.0, 118.2, 122.5, 122.7, 122.9, 125.4, 128.3, 128.6, 128.8, 129.0, 134.8, 136.2, 136.5, 161.4, 190.1. *Anal.* calcd. for $C_{18}H_{17}ClN_2O_2$, %: C, 65.75; H, 5.21; Cl, 10.78; N, 8.52. Found, %: C, 65.54; H, 5.13; Cl, 10.65; N, 8.77.

N-Alkylation of 1-benzyl-1H-benzimidazole with 2-hydroxy-5-(chloromethyl)benzaldehyde 2

Reaction of 5-(chloromethyl)-2-hydroxybenzaldehyde **2** (256 mg, 1.5 mmol) with 1-benzyl-1*H*-benzimidazole (312 mg, 1.5 mmol) in toluene (15 mL) was performed according to the procedure described for the preparation of compound **8** to afford after work-up a solid that was recrystallized twice from 96% ethanol to give 1-benzyl-3-(3-formyl-4-hydroxybenzyl)-1*H*-benzimidazol-3-ium chloride **9** as a colorless solid (122 mg, 16%), m.p. 236–238°C. ^{1}H NMR (DMSO-d_6, 400 MHz), δ (ppm): 5.75 (s, 2H), 5.81 (s, 2H), 7.19 (d, $J = 8.4$ Hz, 1H), 7.33–7.47 (m, 3H), 7.53 (d, $J = 7.2$ Hz, 2H), 7.58–7.70 (m, 2H), 7.74 (dd, $J = 2.4$ and 8.4 Hz, 1H), 7.88 (d, $J = 2.0$ Hz, 1H), 7.92–8.00 (m, 1H), 8.00–8.09 (m, 1H), 10.17 (s, 1H), 10.31 (s, 1H), 11.24 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz), δ (ppm): 49.3, 49.9, 114.0, 114.1,

118.2, 122.5, 124.5, 126.7, 126.8, 128.2, 128.6, 128.7, 129.0, 131.0, 131.1, 134.0, 136.5, 142.7, 161.3, 190.1. *Anal.* calcd. for $C_{22}H_{19}ClN_2O_2$, %: C, 69.75; H, 5.05;Cl, 9.36; N, 7.39. Found, %: C, 69.62; H, 4.97; Cl, 9.58; N, 7.69.

Petasis reaction of 2-hydroxy-5-(isopropoxymethyl)benzaldehyde 4 with phenylboronic acid and morpholine

A solution of 2-hydroxy-5-(isopropoxymethyl)benzaldehyde **4** (388 mg, 2 mmol), phenylboronic acid (244 mg, 2 mmol), and morpholine (174 mg, 2 mmol) in dioxane (10 mL) was heated (oil bath temperature of 100°C) overnight. The solvent was removed under reduced pressure, and then the residue was partitioned between water (30 mL) and dichloromethane (20 mL). The organic layer was collected, and the aqueous layer was further extracted with fresh dichloromethane (20 mL). The combined organic fractions were washed with saturated aqueous NaHCO$_3$ (10 mL), dried over anhydrous Na$_2$SO$_4$, and concentrated to give a residue from which, using flash chromatography (hexanes–ethyl acetate 9:1 v/v), 4-(isopropoxymethyl)-2-[morpholino-(phenyl)methyl]phenol **10** was isolated as a colorless glassy material (423 mg, 62%), R_f 0.23 (hexanes–ethyl acetate 9:1 v/v). ^{1}H NMR (CDCl$_3$, 400 MHz), δ (ppm): 1.16 (d, J = 2.4 Hz, 3H), 1.17 (d, J = 2.4 Hz, 3H), 2.38–2.50 (m, 2H), 2.60 (br s, 2H), 3.62 (sept, 1H), 3.67–3.83 (m, 4H), 4.30 (s, 2H), 4.39 (s, 1H), 6.83 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 2.0 Hz, 1H), 7.11 (dd, J = 2.0 and 8.0 Hz, 1H), 7.22–7.36 (m, 3H), 7.36–7.51 (m, 2H), 11.73 (s, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz), δ (ppm): 22.1 (2 C atoms), 52.3, 66.9, 69.8, 70.9, 76.9, 117.0, 124.5, 128.1, 128.4, 128.5, 128.9, 129.1, 130.0, 139.4, 155.4. *Anal.* calcd. for $C_{21}H_{27}NO_3$, %: C, 73.87; H, 7.97; N, 4.10. Found, %: C, 74.06; H, 8.14; N, 3.89.

Rap–Stoermer reaction of 5-{[(4-chlorophenyl)thio]-methyl}-2-hydroxybenzaldehyde 6 with chloroacetone

A mixture of 5-{[(4-chlorophenyl)thio]methyl}-2-hydroxybenzaldehyde **6** (279 mg, 1 mmol), chloroacetone (111 mg, 1.2 mmol), and anhydrous K$_2$CO$_3$ (276 mg, 2 mmol) in butan-2-one (15 mL) was heated at reflux temperature overnight (17 h). The solvent was removed under reduced pressure, and the residue was partitioned between ethyl acetate (15 mL) and water (15 mL). The organic phase was washed sequentially with water (15 mL) and brine (10 mL), and then it was dried on anhydrous Na$_2$SO$_4$. Removal of the solvent under reduced pressure afforded a material that was recrystallized from 2-propanol to give 1-{5-{[(4-chlorophenyl)thio]methyl}-benzofuran-2-yl}ethanone **11** as a yellow solid (190 mg, 60%), m.p. 111–112°C. ^{1}H NMR (CDCl$_3$, 400 MHz), δ

(ppm): 2.60 (s, 3H), 4.17 (s, 2H), 7.21 (s, 4H), 7.40 (dd, J = 1.6 and 8.8 Hz, 1H), 7.42 (d, J = 0.4 Hz, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 1.2 Hz, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz), δ (ppm): 26.5, 39.4, 112.6, 112.8, 123.1, 127.2, 129.0, 129.3, 131.8, 132.8, 133.1, 134.1, 153.2, 154.9, 188.6. *Anal.* calcd. for $C_{17}H_{13}ClO_2S$, %: C, 64.45; H, 4.14; Cl, 11.19; S, 10.12. Found, %: C, 64.61; H, 4.02; Cl, 11.27; S, 9.93.

Synthesis of 3-acetyl-6-(morpholinomethyl)-2H-chromen-2-one 12

A mixture of 2-hydroxy-5-(morpholinomethyl)benzaldehyde **5** (663 mg, 3 mmol), ethyl acetoacetate (585 mg, 4.5 mmol), and piperidine (10 drops) in 96% ethanol (5 mL) was stirred at room temperature for 3 h, and then the solution was refrigerated overnight. The solid was filtered, washed with a mixture of hexanes−2-propanol (10 mL, 4:1 v/v), and air-dried. Recrystallization from a small volume of 96% ethanol gave yellow crystals (138 mg, 16%), mp 130–131 °C. ^{1}H NMR (DMSO-d_6, 400 MHz), δ (ppm): 2.41 (br s, 4H), 2.59 (s, 3H), 3.60 (br s, 6H), 7.44 (d, J = 8.4 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.88 (s, 1H), 8.64 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz), δ (ppm): 30.0, 52.9, 61.1, 66.0, 116.0, 117.9, 124.5, 130.6, 134.7, 135.2, 147.0, 153.8, 158.4, 195.1. *Anal.* calcd. for $C_{16}H_{17}NO_4$, %: C, 66.89; H, 5.96; N, 4.88. Found, %: C, 66.78; H, 6.06; N, 5.03.

3. Results and Discussion

Chloromethylation of salicylaldehyde has been first reported more than 120 years ago,[28] but a practical synthesis for 5-(chloromethyl)salicylaldehyde has been described only approximately fifty years later.[29] Despite being widely used, the Blanc reaction of salicylaldehyde is known to have a series of shortcomings such as poor reproducibility or broad range of reported yields, which could stem from the co-existence in the final reaction mixture of the target product, of the intermediate carbinol and various side products which could potentially convert into one another under the employed reaction condition,[25] and even from the presence of 3-chloromethylsalicyl-aldehyde as a by-product of chloromethylation.[30] From an experimental point of view, chloromethylation of salicy-laldehyde has been usually performed with formalin, in concentrated aqueous HCl as reaction medium, at room temperature, with reaction times extending up to 48 h. Occasionally, the use of zinc chloride[31] or sulfuric acid[32] as catalysts has been reported. The synthetic procedure employed in this study for the preparation of the starting material was adapted from a published procedure,[33] in which formalin was substituted by paraformaldehyde, owing to the latter's ability to depolymerize under acidic

conditions (Scheme 1). At a 20 mmol scale, the reaction proceeds smoothly to afford variable amounts of crude material for distinct batches. Because it proved to be crucial for the outcome of the reactions in which in the was involved, the purity of intermediate **2** has been verified by recording its proton NMR spectrum, and recrystallization from hexanes was repeated until the sample contained only the desired compound. The ¹H NMR spectrum of 5-(chloromethyl)salicylaldehyde features a singlet integrating for two protons at 4.59 ppm corresponding to the hy-

drogen atoms for the chloromethyl group, another singlet in the offset (δ = 9.90 ppm) that is assigned to the proton of the phenolic hydroxyl involved in a hydrogen bond with the oxygen atom from the neighboring carbonyl function, and only three aromatic protons associated the hydrogen atoms in the phenyl moiety. In the carbon NMR, the only peak in the aliphatic region (δ = 45.4 ppm) is indicative for the presence of the carbon atom in the chloromethyl function attached through the Blanc reaction to the aromatic ring in salicylaldehyde.
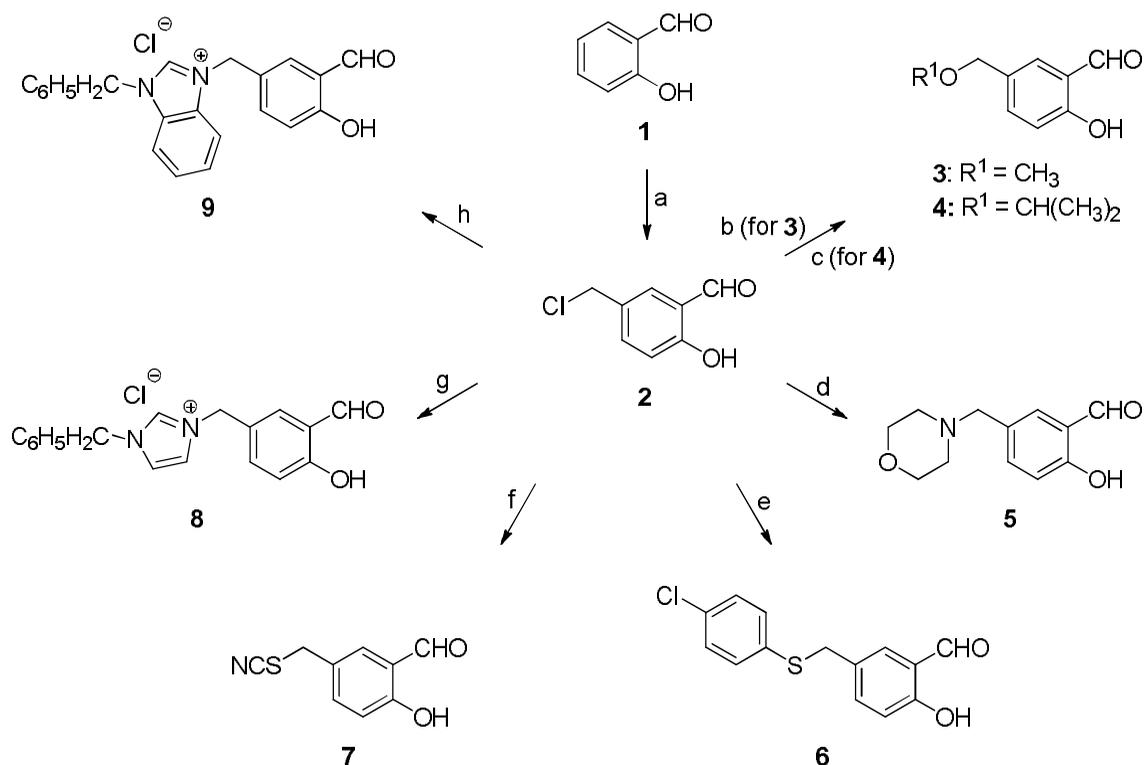
Scheme 1. Synthesis of 5-(chloromethyl)salicylaldehyde and its conversion into other *ortho*-hydroxybenzaldehydes through nucleophilic substitution of chlorine by nucleophiles: **a)** paraformaldehyde, aq. 36.5% HCl, r.t., 24 h, 38–48%; **b)** 1. methanol, NaHCO₃, r.t., 4 h, then 50°C, 4 h; 2. Amberjet 1200(H), acetone, water, r.t., 5 h, 49%; **c)** 2-propanol, NaHCO₃, r.t., 18 h, then 50°C, 4 h, 96%; **d)** morpholine, K₂CO₃, acetone, r.t., 18 h, 57%; **e)** 4-chlorothiophenol, chloroform, NaHCO₃, r.t., 18 h, 58%; **f)** KSCN, acetone, r.t., 18 h, 43%; **g)** 1-benzyl-1*H*-imidazole, toluene, 70°C, 24 h, 60%; **h)** 1-benzyl-1*H*-benzimidazole, toluene, 70°C, 24 h, 16%

The preparation of a series of intermediates through the replacement of the chlorine in the compound **2** with various nucleophiles was then investigated with a view to subsequently examine the suitability of these novel salicylaldehydes as substrates in a few organic reactions. First, the reaction of 5-(chloromethyl)salicylaldehyde **2** with selected alcohols was examined, a type of chemical process that has been reported scarcely in literature, for example for the reaction with hexaethylene glycol,[33] 2-[(adamantan-1-yl)oxy]ethanol,[34] or low molecular weight alcohols.[35] In particular, key intermediate **2** was reacted in

a straightforward manner with either methanol or 2-propanol to give alkoxymethyl-salicylaldehydes **3** and **4**, respectively (Scheme 1). A large excess of alcohol was employed with the view to fully convert the starting material **2** into the target compounds **3** and **4**, while a mild base such as NaHCO₃ rather than a strong base such an alkali hydroxide was used in order to avoid secondary transformations, *i.e.*, the self *O*-alkylation of 5-(chloromethyl)salicylaldehyde.[36] The synthesis of these two compounds was reported previously under more elaborate reaction conditions,[35] but the resulting compounds **3** and **4**

have not been structurally characterized. While *O*-alkylation of 2-propanol with 5-(chloromethyl)salicylaldehyde **2** gave after work-up only the expected compound **4** that was deemed by NMR to be sufficiently pure for most practical purposes, the similar reaction of intermediate **2** with methanol afforded initially a 1:5 mixture of the desired aldehyde **3** (minor component) and its corresponding dimethyl acetal (major component). Deprotection of the acetal in this mixture was performed directly using the method reported by Coppola,[37] which gave in the end the practically pure compound **3**. Although the crude mixture comprising aldehyde **3** and its acetal was isolated with a good 71% yield (equivalent to the theoretical amount of compound **3**), the additional step of acetal hydrolysis reduced the yield further. NMR analysis of these two 5-(alkoxymethyl)salicylaldehydes showed that replacement of the chlorine with alkoxy moieties was accompanied by a slight change of the chemical shift value of the singlet corresponding to the protons in the methylene group adjacent to the aromatic ring from 4.59 ppm to 4.42 ppm in the case of compound **3**, and to 4.47 ppm for compound **4**, while the conversion of **2** into either **3** or **4** led to more pronounced modification of the chemical shift value of the peak corresponding to the carbon atom of the same methylene group. The correct signals for the newly introduced alkoxy moieties could be attributed in the aliphatic region of the proton and carbon NMR spectra, namely a singlet integrating for three protons at $\delta = 3.40$ ppm and a peak at 73.7 ppm for compound **3**, and a doublet integrating for six protons at $\delta = 1.23$ ppm, a septet integrating for one proton at $\delta = 3.70$ ppm, and the peaks at 22.1 ppm and 71.3 ppm for compound **4**.

Despite the fact that 5-(*N,N*-disubstituted aminomethyl)salicyladehydes have been reported as reagents in various chemical transformation, their preparation through *N*-alkylation of secondary aliphatic amines with 5-(chloromethyl)salicylaldehyde **2** has been scarcely described in the literature.[38–40] In order to explore the synthesis of a member of this particular group of salicylaldehydes, 2-hydroxy-5-(morpholinomethyl)benzaldehyde **5** has been chosen as the target compound, and an approach distinct in terms of reaction conditions (solvent, base, reaction temperature, and reaction time) from the ones frequently mentioned in the literature has been examined (Scheme 1). Specifically, morpholine and the alkylating agent **2** were stirred in acetone, in the presence of K_2CO_3, at room temperature overnight, and work-up of the reaction mixture afforded the desired compound sufficiently pure for use in subsequent chemical transformations, albeit in moderate yield compared to those already reported. Therefore, the synthetic approach reported in this study

for the preparation of compound **5** is inferior in terms of yield to those employing triethylamine in refluxing toluene (91% yield)[26] or K_2CO_3 in refluxing acetonitrile (also 91% yield).[39] The presence of the morpholine moiety in the structure of aldehyde **5** was confirmed by the identification in its proton NMR spectrum of a triplet at 2.32 ppm that was assigned to the hydrogen atoms of the methylene groups adjacent to nitrogen, and also of a second triplet at 3.55 pm that was associated with the hydrogen atoms of the methylene groups adjacent to oxygen, while the peaks at 53.0 ppm and 66.2 ppm in the carbon NMR spectrum were attributed to the carbon atoms in the same methylene groups of the morpholine moiety in compound **5**.

Next, our focus shifted towards the use of sulfur nucleophiles for the replacement of the halogen atom in 5-(chloromethyl)salicylaldehyde **2**. While this study was underway, a report that described the synthesis of several 5-[(arylthio)methyl]salicylaldehydes using KOH in ethanol at reflux temperature became publicly available.[27] A few attempts at replicating the published procedure using 4-chlorothiophenol as the sulfur nucleophile showed that it was not entirely reliable, as it sometimes (but not always) produced mixtures of reaction products from which the desired compound could no longer be isolated in pure form even after repeated recrystallization. Analysis of the mixture of reaction products by NMR indicated that at least two impurities were also phenolic aldehydes, which were presumably generated through the concurrent self-condensation *via O*-alkylation of the starting aldehyde **2** under the reaction conditions,[36] possibly followed by replacement of the terminal chlorine atom in the resulting dimer of 5-(chloromethyl)salicylaldehyde by one of present nucleophiles (4-chlorothiophenol, or ethanol, or water). Building on our previous successful alkylation of oxygen and nitrogen nucleophiles with using 5-(chloromethyl)salicylaldehyde in the presence of a base weaker than KOH, a milder alternative for the preparation of compound **6** that avoided the use of strong alkali as base and that of ethanol as the solvent, was developed. Thus, the *S*-alkylation of 4-chlorothiophenol with key intermediate **2** in the presence of $NaHCO_3$ in chloroform at room temperature overnight afforded in a trouble-free manner the pure aldehyde **6** in fairly good yield (Scheme 1). It should be mentioned that the yields recorded for this approach were only marginally lower than those obtained in our only two successful attempts that used the published procedure; these yields were in the range of 75 to 80% for the crude isolated product and approximately 65% for the pure compound **6** (Sanad and Mekky reported a yield of 88% for the same compound,[27] supposedly after one recrystallization from ethanol). In-

spection of the information gathered from the NMR spectra of aldehyde **6** that was recorded in CDCl$_3$ (the data provided in the literature[27] were obtained from a sample dissolved in DMSO-d_6) was in perfect agreement with its structure. In addition to 4-chlorothiophenol, the use of thiocyanate anion for the replacement of chlorine in 5-(chloromethyl)salicylaldehyde with a sulfur nucleophile was also examined. Taking advantage of the excellent solubility of KSCN in acetone, its reaction with key intermediate **2** was performed in this solvent at room temperature overnight. In the crude reaction product (which was isolated in a fairly good yield of 84% relative to the theoretical amount), the desired aldehyde **7** was accompanied by another salicyladehyde as the major by-product (approximately 10% by NMR, it was not further isolated and characterized). The pure compound was obtained after extraction and repeated recrystallization, a series of operations that lowered the yield. As it was also the case for the sulfur-containing salicylaldehyde **6**, the singlet corresponding to the two protons of the methylene group in the proton spectrum of compound **7** was downfield compared to the similar singlet in the proton spectrum of the starting material **2**. The presence of the thiocyano function in the structure of was further substantiated by the association of the peak at 111.5 ppm in the ^{13}C NMR spectrum of aldehyde **7** with the quaternary carbon atom in this group.

Quaternization of 1-substituted imidazoles leads to salts with ionic liquid behavior that exhibit significant antimicrobial properties.[41] The presence of the reactive hydroxy and formyl functions in the substituent of such quaternized heterocycles would further allow their chemical modification for other important applications.[42–44] So far, to the best of our knowledge, mostly 1-alkylimidazoles have been *N*-alkylated with 5-(chloromethyl)salicylaldehyde; the present study broadens this particular family of imidazolium salts through the inclusion of the product **8** resulted from the *N*-alkylation of 1-benzyl-1*H*-imidazole with key intermediate **2** (Scheme 1). The use of a reported synthetic procedure[45] gave a quantitative yield of the desired compound, but the purification of the crude product through recrystallization occurred with substantial loss of material. ^{1}H NMR spectrum of salicylaldehyde **8** presented two singlets integrating for two protons close to 5.4 ppm, which correspond to the aliphatic hydrogens in the magnetically non-equivalent benzylic groups, while the easily discernible singlet at 9.42 ppm can be unmistakably associated with the deshielded proton at C-2 in the imidazolium ring. Because a literature search revealed the scarcity of benzimidazolium salts bearing as a substituent at one of its nitrogen atoms a

moiety derived from salicylaldehyde, the benzofused analog **9** was also synthesized (Scheme 1). Under identical reaction conditions as those employed for the preparation of imidazolium salt **8**, *N*-alkylation of 1-benzyl-1*H*-benzimidazole with 5-(chloromethyl)salicylaldehyde was less straightforward than that of 1-benzyl-1*H*-imidazole, as it produced a lower yield of a crude material (53% equated to pure compound **9**). This outcome could be indicative of a diminished reactivity of 1-benzyl-1*H*-benzimidazole in this reaction compared to that of imidazole analog. Moreover, the material isolated from this reaction contained a small amount of an impurity that was not soluble in ethanol and had to be removed by filtration. In addition, repeated recrystallization of the remaining substance was required in order to afford the target compound **9** in pure form, which resulted in a poor yield of only 16%. NMR structural investigation of this compound also revealed two singlets integrating for two hydrogen atoms in the aliphatic region of the proton spectrum, but these singlets were more deshielded than the similar signals recorded for analogous **8**, as they were identified at chemical shift values close to 5.8 ppm. Again, the distinct singlet for the proton at C-2 in the benzimidazolium ring system was plainly noticeable in the vicinity of 10 ppm of the proton spectrum of salicylaldehyde **9**.

The reactivity of a few of the salicyaldehydes whose synthesis has been presented in this study was also investigated. The recent reports on the biological activity of aminobenzylated phenols[46,47] and our longtime interest in the chemistry and applications of Mannich bases prompted the examination of the potential use of aldehyde **4** as reagent in a Petasis borono-Mannich reaction with phenylboronic acid and morpholine (Scheme 2). A procedure for the Petasis reaction adapted from a literature method[48] afforded the aminobenzylated phenol **10** in good yield after column chromatography. Structural NMR characterization of Mannich base **10** made use of two-dimensional NMR spectroscopy to facilitate the identification in the spectrum of the protons in the isopropoxy moiety (two doublets at 1.6–1.7 ppm and a septet centered at 3.62 ppm), in the morpholine ring (four protons in methylene groups adjacent to nitrogen in the range 2.38–2.67 ppm and four protons in methylene groups adjacent to oxygen in the range 3.67–3.83 ppm), and at the tertiary carbon atom (4.39 ppm) originating from the formyl function in starting material **4**. Only the proton of the phenolic hydroxyl was noticeable in the off-set of the spectrum, while the correct number of aromatic protons in the structure of compound **10** was found in the aromatic region of the spectrum.
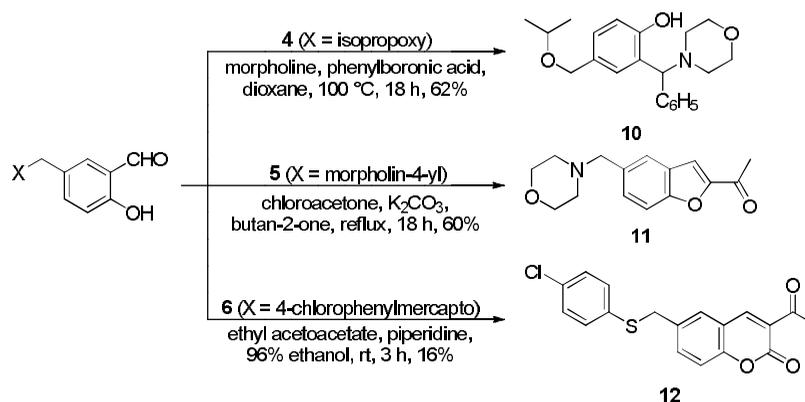
Scheme 2. Salicylaldehydes **4–6** as starting materials in the Petasis reaction and in heterocyclic synthesis

Heterocycle formation through ring closure involving the spatially proximal hydroxyl and formyl groups in the structure of 2-hydroxybenzaldehydes was also explored using a couple of salicylaldehydes whose synthesis has been presented in this study. First, aldehyde **6** was used as substrate for the preparation of sulfur-containing benzofuran **11** *via* cyclocondensation with chloroacetone (Scheme 2). No signals could be found in the off-set of the proton NMR spectrum of compound **10**, which indicates the absence of the phenolic proton and the inclusion of the formyl group into the benzofuran ring system as the tertiary carbon atom C-3, whose proton has been associated with the doublet at 7.42 ppm using correlation spectroscopy. The chemical shift values for the protons (appearing as a singlet at 2.60 ppm) and for the carbon atoms (26.5 ppm for the carbon in the methyl group and 188.6 ppm for the carbon in the carbonyl group) of the acetyl function in benzofuran **11** are comparable with the corresponding values in similar 2-acetylbenzofurans described in the literature.[49] The peaks of the quaternary aromatic carbon atoms adjacent to oxygen have also been identified in the ^{13}C NMR spectrum of benzofuran **11**, and were assigned the signals at 153.2 ppm for the carbon in the junction of the benzene and furan rings and at 154.9 ppm for acetyl-substituted carbon in the furan ring.

Cyclocondensation of salicylaldehyde **5** with ethyl acetoacetate serves as the second example for the involvement of spatially proximal hydroxyl and formyl groups in the synthesis of heterocycles through ring closure (Scheme 2). A conventional procedure[50] was employed to prove the feasibility of the ring closure using an amine-substituted salicylaldehyde as substrate. This approach led to the isolation of a small amount of crude 2-acetylcoumarin **12** (33%), which was further halved owing to compound's good solubility in the recrystallization solvent. No optimization of the process was attempted at this stage, but improvement of the reaction conditions (*e.g.*, through the use of smaller volumes of solvent in the synthesis, of elevated reaction temperature, or of a longer reaction

time) along with a more careful selection of the solvent in the purification stage should markedly increase the yield. The success of the reaction was confirmed by the absence in the off-set of the proton spectrum of compound **12** of the signal for the phenolic proton and by the incorporation of the formyl group from the starting aldehyde **5** into the benzopyran ring system as the tertiary carbon atom C-4, whose proton has been assigned the singlet at 8.64 ppm using two-dimensional NMR spectroscopy. The presence in ^{1}H NMR spectrum of compound **12** of the signals corresponding to the protons of the acetyl group (a singlet integrating for three hydrogens at 2.59 ppm) and to the protons of the morpholine moiety (a broad singlet at 2.41 ppm for the four hydrogens in the methylene groups adjacent to nitrogen and a broad singlet at 3.60 ppm for four hydrogens in the methylene groups adjacent to oxygen, which was superimposed with the signal for the hydrogens of the methylene group bridging morpholine and benzopyran moieties) was also established. The presence of two distinct peaks in the ^{13}C NMR spectrum of compound **12** for the carbon atoms of the carbonyl functions (195.1 ppm for the carbon in acetyl and 158.4 ppm for C-2 in the 2-oxochromene scaffold) further provided evidence for the heterocyclic structure of compound **12** by comparison with the spectra of other 3-acetylcoumarins.[51]

4. Conclusions

Several salicylaldehydes were synthesized through the nucleophilic substitution of chlorine in 5-(chloromethyl)salicylaldehyde. Detailed experimental procedures and optimized reaction conditions have been presented for a few reported, yet so far little known members of this collection of 2-hydroxybenzaldehydes. A number of hitherto unknown salicylaldehydes have also been disclosed, while the use of selected compounds in this small library of 2-hydroxybenzaldehydes in the successful synthesis of a 2-acetylbenzofuran, a 3-acetylcoumarin deriva-

tive, and an aminobenzylated phenol *via* the Petasis reaction was demonstrated. NMR analysis was shown to be an effective tool for the characterization of the novel compounds and for pinpointing their typical structural features.

References

[1] Masesane, I.B.; Desta, Z.Y. Reactions of Salicylaldehyde and Enolates or Their Equivalents: Versatile Synthetic Routes to Chromane Derivatives. *Beilstein J. Org. Chem.* **2012**, *8*, 2166-2175. https://doi.org/10.3762/bjoc.8.244

[2] Sebastian, A.; Srinivasulu, V.; Abu-Yousef, I.A.; Gorka, O.; Al-Tel, T.H. Domino Transformations of Ene/Yne Tethered Salicylaldehyde Derivatives: Pluripotent Platforms for the Construction of High sp³ Content and Privileged Architectures. *Chem. – Eur. J.* **2019**, *25*, 15710-15735. https://doi.org/10.1002/chem.201902596

[3] Sheykhi, S.; Pedrood, K.; Amanlou, M.; Larijani, B.; Mahdavi, M. Synthesis of Chromene-Fused Heterocycles by the Intramolecular–Diels–Alder Reaction: An Overview. *Tetrahedron* **2021**, *102*, 132524. https://doi.org/10.1016/j.tet.2021.132524

[4] Koca, M.; Ertürk, A.S.; Bozca, O. Rap-Stoermer Reaction: TEA Catalyzed One-Pot Efficient Synthesis of Benzofurans and Optimization of Different Reaction Conditions. *ChemistrySelect* **2022**, 7, e202202243. https://doi.org/10.1002/slct.202202243

[5] Phan, P.-T.T.; Nguyen, T.-T.T.; Nguyen, H.-N.T.; Le, B.-K.N.; Vu, T.T.; Tran, D.C.; Pham, T.-A.N. Synthesis and Bioactivity Evaluation of Novel 2-Salicyloylbenzofurans as Antibacterial Agents. *Molecules* **2017**, *22*, 687. https://doi.org/10.3390/molecules22050687

[6] Zhang, H.; Yan, Y.; Li, Y.; Gao, W. A Facile Synthesis of Novel Benzofuran-2-yl(9-methyl-9*H*-carbazol-3-yl)methanones. *Res. Chem. Intermed.* **2012**, *38*, 1909-1919. https://doi.org/10.1007/s11164-012-0513-1

[7] Dale, T.J.; Sather, A.C.; Rebek Jr., J. Synthesis of Novel Aryl-1,2-oxazoles from *ortho*-Hydroxyaryloximes. *Tetrahedron Lett.* **2009**, *50*, 6173-6175. https://doi.org/10.1016/j.tetlet.2009.08.086

[8] Kalkhambkar, R.G.; Yuvaraj, H. Triflic Anhydride: A Mild Reagent for Highly Efficient Synthesis of 1,2-Benzisoxazoles, Isoxazolo, and Isothiazolo Quinolines Without Additive or Base. *Synth. Commun.* **2014**, *44*, 547-555. https://doi.org/10.1080/00397911.2013.821617

[9] Iranpoor, N.; Firouzabadi, H.; Nowrouzi, N. A Novel Method for the Highly Efficient Synthesis of 1,2-Benzisoxazoles under Neutral Conditions Using the Ph₃P/DDQ System. *Tetrahedron Lett.* **2006**, *47*, 8247-8250. https://doi.org/10.1016/j.tetlet.2006.09.120

[10] Tkachenko, V.V.; Muravyova, E.A.; Desenko, S.M.; Shishkin, O.V.; Shishkina, S.V.; Sysoiev, D.O.; Müller T.J.J.; Chebanov, V.A. The Unexpected Influence of Aryl Substituents in *N*-Aryl-3-Oxobutanamides on the Behavior of Their Multicomponent Reactions with 5-Amino-3-Methylisoxazole and Salicylaldehyde. *Beilstein J. Org. Chem.* **2014**, *10*, 3019-3030. https://doi.org/10.3762/bjoc.10.320

[11] Voskressensky, L.G.; Festa, A.A.; Varlamov, A.V. Domino Reactions Based on Knoevenagel Condensation in the Synthesis of Heterocyclic Compounds. Recent Advances. *Tetrahedron* **2014**, *70*, 551-572. https://doi.org/10.1016/j.tet.2013.11.011

[12] Wu, P.; Givskov, M.; Nielsen, T.E. Reactivity and Synthetic Applications of Multicomponent Petasis Reactions. *Chem. Rev.* **2019**, *119*, 11245-11290. https://doi.org/10.1021/acs.chemrev.9b00214

[13] Candeias, N.R.; Montalbano, F.; Cal, P.M.S.D.; Gois, P.M.P. Boronic Acids and Esters in the Petasis-Borono Mannich Multicomponent Reaction. *Chem. Rev.* **2010**, *110*, 6169–6193. https://doi.org/10.1021/cr100108k

[14] Andruh, M. The Exceptionally Rich Coordination Chemistry Generated by Schiff-Base Ligands Derived from *o*-Vanillin. *Dalton Trans.* **2015**, *44*, 16633-16653. https://doi.org/10.1039/c5dt02661j

[15] Mazzoni, R.; Roncaglia, F.; Rigamonti, L. When the Metal Makes the Difference: Template Syntheses of Tridentate and Tetradentate Salen-Type Schiff Base Ligands and Related Complexes. *Crystals* **2021**, *11*, 483. https://doi.org/10.3390/cryst11050483

[16] Enyedy, É.A.; Petrasheuskaya, T.V.; Kiss, M.A.; Wernitznig, D.; Wenisch, D.; Keppler, B.K.; Spengler, G.; May, N.V.; Frank, É.; Dömötör, O. Complex Formation of an Estrone-Salicylaldehyde Semicarbazone Hybrid with Copper(II) and Gallium(III): Solution Equilibria and Biological Activity. *J. Inorg. Biochem.* **2021**, *220*, 111468. https://doi.org/10.1016/j.jinorgbio.2021.111468

[17] Sako, M.; Takizawa, S.; Sasai, H. Chiral Vanadium Complex-Catalyzed Oxidative Coupling of Arenols. *Tetrahedron* **2020**, *76*, 131645. https://doi.org/10.1016/j.tet.2020.131645

[18] Berhanu, A.L.; Gaurav; Mohiuddin, I.; Malik, A.K.; Aulakh, J.S.; Kumar, V.; Kim, K.-H. A Review of the Applications of Schiff Bases as Optical Chemical Sensors. *TrAC – Trends Anal. Chem.* **2019**, *116*, 74-91. https://doi.org/10.1016/j.trac.2019.04.025

[19] Zhong, T.; Jiang, N.; Li, C.; Wang, G. A Highly Selective Fluorescence and Absorption Sensor for Rapid Recognition and Detection of Cu²⁺ Ions in Aqueous Solution and Film. *Luminescence* **2022**, *37*, 391-398. https://doi.org/10.1002/bio.4180

[20] Ganesan, G.; Pownthurai, B.; Kotwal, N.K.; Yadav, M.; Chetti, P.; Chaskar, A. Function-Oriented Synthesis of Fluorescent Chemosensor for Selective Detection of Al³⁺ in Neat Aqueous Solution: Paperstrip Detection & DNA Bioimaging. *J. Photochem. Photobiol. A Chem.* **2022**, *425*, 113699. https://doi.org/10.1016/j.jphotochem.2021.113699

[21] Sun, Y.; Lu, Y.; Bian, M.; Yang, Z.; Ma, X.; Liu, W. Pt(II) and Au(III) Complexes Containing Schiff-base Ligands: A Promising Source for Antitumor Treatment. *Eur. J. Med. Chem.* **2021**, *211*, 113098. https://doi.org/10.1016/j.ejmech.2020.113098

[22] Tanaka, T.; Tsurutani, K.; Komatsu, A.; Ito, T.; Iida, K.; Fujii, Y.; Nakano, Y.; Usui, Y.; Fukuda, Y.; Chikira, M. Synthesis of New Cationic Schiff Base Complexes of Copper(II) and Their Selective Binding with DNA. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 615-629. https://doi.org/10.1246/bcsj.70.615

[23] Chew, S.T.; Lo, K.M.; Lee, S.K.; Heng, M.P.; Teoh, W.Y.; Sim, K.S.; Tan, K.W. Copper Complexes with Phosphonium Containing Hydrazone Ligand: Topoisomerase Inhibition and Cytotoxicity Study. *Eur. J. Med. Chem.* **2014**, *76*, 397-407. https://doi.org/10.1016/j.ejmech.2014.02.049

[24] Akkoç, S.; Kayser, V.; İlhan, İ.Ö. Synthesis and *in vitro* Anticancer Evaluation of Some Benzimidazolium Salts. *J. Heterocycl. Chem.* **2019**, *56*, 2934-2944. https://doi.org/10.1002/jhet.3687

[25] Kadwa, E.; Friedrich, H.B.; Bala, M.D. Structural Identification of Products from the Chloromethylation of Salicylaldehyde. *Synlett* **2019**, *30*, 44-48. https://doi.org/10.1055/s-0037-1610334

[26] Shaker, M.; Beni, A.S. Cu@SB-MCM-41 Composite as an Efficient and Recyclable Nanocatalyst for the Synthesis of Polyhydroquinoline Derivatives *via* Unsymmetrical Hantzsch Reaction. *J. Porous Mater.* **2021**, *28*, 435-449. https://doi.org/10.1007/s10934-020-01006-8

[27] Sanad, S.M.H.; Mekky, A.E.M. Efficient Synthesis and Characterization of Novel *bis*-Heterocyclic Derivatives and Benzo-Fused Macrocycles Containing Oxazolone or Imidazolone Subunits. *J. Heterocycl. Chem.* **2020**, *57*, 3930-3942. https://doi.org/10.1002/jhet.4102

[28] Stoermer, R.; Behn, K. Synthese Aromatischer Alkohole mit Formaldehyd. *Ber. Dtsch. Chem. Ges.* **1902**, *34*, 2455-2460. https://doi.org/10.1002/cber.190103402188

[29] Angyal, S.J.; Morris, P.J.; Tetaz, J.R.; Wilson, J.G. The Sommelet Reaction. Part III. The Choice of Solvent and the Effect of Substituents. *J. Chem. Soc.* **1950**, *1950*, 2141-2145. https://doi.org/10.1039/JR9500002141

[30] Wei, Z.; Bi, H.; Liu, Y.; Nie, H.; Yao, L.; Wang, S.; Yang, J.; Wang, Y.; Liu, X.; Zheng, Z. Design, Synthesis and Evaluation of New Classes of Nonquaternary Reactivators for Acetylcholinesterase Inhibited by Organophosphates. *Bioorg. Chem.* **2018**, *81*, 681-688. https://doi.org/10.1016/j.bioorg.2018.09.025

[31] Elshaarawy, R.F.M.; Mostafa, T.B.; Refaee, A.A.; El-Sawi, E.A. Ionic Sal-SG Schiff Bases as New Synergetic Chemotherapeutic Candidates: Synthesis, Metalation with Pd(II) and *in vitro* Pharmacological Evaluation. *RSC Adv.* **2015**, *5*, 68260-68269. https://doi.org/10.1039/C5RA11083A

[32] Ghamari Kargar, P.; Noorian, M.; Chamani, E.; Bagherzade, G.; Kiani, Z. Synthesis, Characterization and Cytotoxicity Evaluation of a Novel Magnetic Nanocomposite with Iron Oxide Deposited on Cellulose Nanofibers with Nickel (Fe$_3$O$_4$@NFC@ONSM-Ni). *RSC Adv.* **2021**, *11*, 17413-17430. https://doi.org/10.1039/D1RA01256H

[33] Dalla Cort, A.; Mandolini, L.; Pasquini, C.; Schiaffino, L. A Novel Ditopic Zinc-Salophen Macrocycle: A Potential Two-Stationed Wheel for [2]-Pseudorotaxanes. *Org. Biomol. Chem.* **2006**, *4*, 4543-4546. https://doi.org/10.1039/B613705A

[34] Forte, G.; Maglione, M.S.; Tulli, L.G.; Fantoni, A.; Dalla Cort, A. A Newly Designed Water Soluble Uranyl-Salophen Complex for Anion Recognition. *ChemistryOpen* **2021**, *10*, 848-851. https://doi.org/10.1002/open.202100182

[35] Ho, C.-Y. Cyanative Alkene–Aldehyde Coupling: Ni(0)–NHC–Et$_2$AlCN Mediated Chromanols Synthesis with High *cis*-Selectivity at Room Temperature. *Chem. Commun.* **2010**, *46*, 466-468. https://doi.org/10.1039/B918626C

[36] Kazemnejadi, M.; Shakeri, A.; Mohammadi, M.; Tabefam, M. Direct Preparation of Oximes and Schiff Bases by Oxidation of Primary Benzylic or Allylic Alcohols in the Presence of Primary Amines Using Mn(III) Complex of Polysalicylaldehyde as an Efficient and Selective Heterogeneous Catalyst by Molecular Oxygen. *J. Iran. Chem. Soc.* **2017**, *14*, 1917-1933. https://doi.org/10.1007/s13738-017-1131-z

[37] Coppola, G. M. Amberlyst-15, a Superior Acid Catalyst for the Cleavage of Acetals. *Synthesis* **1984**, *1984*, 1021-1023. https://doi.org/10.1055/s-1984-31059

[38] Meléndez, J.; North, M.; Villuendas, P. One-Component Catalysts for Cyclic Carbonate Synthesis. *Chem. Commun.* **2009**, *2009*, 2577-2579. https://doi.org/10.1039/B900180H

[39] Wei, X.; Li, J.; Zhou, B.; Qin, S. Synthesis, Oxygenation and Catalytic Epoxidation Performance of Salen and Salophen Transition-Metal Complexes with Aza-Crown or Morpholino Pendants. *Transition Met. Chem.* **2004**, *29*, 457-462. https://doi.org/10.1023/B:TMCH.0000027463.00158.6b

[40] Bagherzadeh, M.; Zare, M. Synthesis, Characterization and Catalysis of Recyclable New Piperazine-Bridged Mo(VI) Polymers [MoO$_2$(Salen) (Piperazine)]$_n$ in Highly Selective Oxygenation of Alkenes and Sulfides. *J. Coord. Chem.* **2013**, *66*, 2885-2900. https://doi.org/10.1080/00958972.2013.818671

[41] Docherty, K.M.; Kulpa, Jr., C.F. Toxicity and Antimicrobial Activity of Imidazolium and Pyridinium Ionic Liquids. *Green Chem.* **2005**, *7*, 185-189. https://doi.org/10.1039/B419172B

[42] Modak, R.; Mondal, B.; Howlader, P.; Mukherjee, P.S. Self-Assembly of a "Cationic-Cage": *Via* the Formation of Ag-Carbene Bonds Followed by Imine Condensation. *Chem. Commun.* **2019**, *55*, 6711-6714. https://doi.org/10.1039/C9CC02341K

[43] Boldescu, V.; Sucman, N.; Hassan, S.; Iqbal, J.; Neamtu, M.; Lecka, J.; Sévigny, J.; Prodius, D.; Macaev, F. Ectonucleotidase Inhibitory and Redox Activity of Imidazole-Based Organic Salts and Ionic Liquids. *ChemMedChem,* **2018**, *13*, 2297-2304. https://doi.org/10.1002/cmdc.201800520

[44] Lecarme, L.; Prado, E.; De Rache, A.; Nicolau-Travers, M.-L.; Bonnet, R.; van der Heyden, A.; Philouze, C.; Gomez, D.; Mergny, J.-L.; Jamet, H.; *et al.* Interaction of Polycationic Ni(II)-Salophen Complexes with G-Quadruplex DNA. *Inorg. Chem.* **2014**, *53*, 12519-12531. https://doi.org/10.1021/ic502063r

[45] Elshaarawy, R.F.M.; Tadros, H.R.Z.; Abd El-Aal, R.M.; Mustafa, F.H.A.; Soliman, Y.A.; Hamed, M.A. Hybrid Molecules Comprising 1,2,4-Triazole or Diaminothiadiazole Schiff-Bases and Ionic Liquid Moieties as Potent Antibacterial and Marine Antibiofouling Nominees. *J. Environ. Chem. Eng.* **2016**, *4*, 2754-2764. https://doi.org/10.1016/j.jece.2016.05.016

[46] Neto, Í.; Andrade, J.; Fernandes, A.S.; Pinto Reis, C.; Salunke, J.K.; Priimagi, A.; Candeias, N.R.; Rijo, P. Multicomponent Petasis-Borono Mannich Preparation of Alkylaminophenols and Antimicrobial Activity Studies. *ChemMedChem* **2016**, *11*, 2015-2023. https://doi.org/10.1002/cmdc.201600244

[47] Doan, P.; Karjalainen, A.; Chandraseelan, J.G.; Sandberg, O.; Yli-Harja, O.; Rosholm, T.; Franzen, R.; Kandhavelu, M. Synthesis and Biological Screening for Cytotoxic Activity of *N*-Substituted Indolines and Morpholines. *Eur. J. Med. Chem.* **2016**, *120*, 296-303. https://doi.org/10.1016/j.ejmech.2016.05.024

[48] Wang, Q.; Finn, M. G. 2*H*-Chromenes from Salicylaldehydes by a Catalytic Petasis Reaction. *Org. Lett.* **2000**, *2*, 4063-4065. https://doi.org/10.1021/ol006710r

[49] Paizs, C.; Toşa, M.; Majdik, C.; Moldovan, P.; Novák, L.; Kolonits, P.; Marcovici, A.; Irimie, F.-D.; Poppe, L. Optically Active 1-(Benzofuran-2-yl)ethanols and Ethane-1,2-diols by Enantiotopic Selective Bioreductions. *Tetrahedron Asymmetry* **2003**, *14*, 1495-1501. https://doi.org/10.1016/S0957-4166(03)00222-2

[50] Alizadeh, A.; Ghanbaripour, R. An Efficient Synthesis of Pyrrolo[2,1-*a*]isoquinoline Derivatives Containing Coumarin Skeletons *via* a One-Pot, Three-Component Reaction. *Res. Chem. Intermed.* **2015**, *41*, 8785-8796. https://doi.org/10.1007/s11164-015-1928-2

[51] Villa-Martínez, C.A.; Magaña-Vergara, N.E.; Rodríguez, M.; Mojica-Sánchez, J.P.; Ramos-Organillo, Á.A.; Barroso-Flores, J.; Padilla-Martinez, I.I.; Martínez-Martínez, F.J. Synthesis, Optical Characterization in Solution and Solid-State, and DFT Calculations of 3-Acetyl and 3-(1′-(2′-Phenylhydrazono)ethyl)-coumarin-(7)-substituted Derivatives. *Molecules* **2022**, *27*, 3677. https://doi.org/10.3390/molecules27123677

САЛІЦИЛОВІ АЛЬДЕГІДИ, ОТРИМАНІ З 2-ГІДРОКСИ-5-ХЛОРОМЕТИЛБЕНЗАЛЬДЕГІДУ: СИНТЕЗ І РЕАКЦІЇ

Анотація. Синтезовано ряд саліцилових альдегідів заміщенням хорошої відхідної групи – атома хлору – у 2-гідрокси-5-хлорометилбензальдегіді різними О-, S- або N-нуклеофілами. Досліджено участь деяких із цих саліцилових альдегідів у синтезі гетероциклів, таких як бензофуран або кумарин, а також застосування їх як субстрату в реакції Петасіса бороно-Манніха.

Ключові слова: *2-гідроксибензальдегіди, нуклеофільне заміщення, ЯМР аналіз, синтез гетероциклів, реакція Петасіса.*