One-Pot Synthesis of Heterocyclic β-Chlorovinyl Aldehydes Using Vilsmeier Reagent

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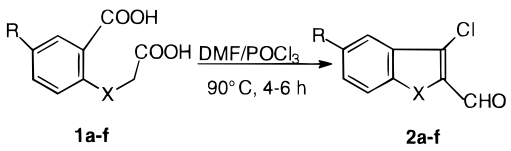
3-Chloro-1*H*-indole-2-carboxaldehydes are obtained in moderate yields by the one-pot reaction of various substituted 2-[(carboxymethyl)amino]benzoic acids (**1a**−**d**) using Vilsmeier reagent (DMF/$POCl_3$). The benzfused acyclic diacids analogous to **1a** in which nitrogen was replaced by oxygen and sulfur also underwent the reaction smoothly. 3-Chloro-1*H*-pyrrole-2,4-dicarboxaldehyde was obtained as the only product by the reaction of *N*-carboxymethyl β-alanine.

β-Chlorovinyl aldehydes[1] are versatile intermediates in organic synthesis. There is a wealth of patent literature on the use of the 2-carboxaldehydes of five-membered benzfused heterocycles in the preparation of lipoxygenase inhibitors,[2a] antitumor agents,[2b] psychotropics,[2c] organoleptic agents,[2d] serotoninergic antagonist pyrimidoindolone derivatives,[2e] and fungicides[2f] among other drug classes.

Recently, we have been attempting to exploit the cyclization potential of halomethyleniminium salts for developing new strategies toward the synthesis of heterocyclic compounds.[3] The halomethyleniminium salts which are the intermediates involved in the Vilsmeier−Haack−Arnold reaction are extensively used for formylation[4] of activated aromatic compounds and carbonyl compounds. The Vilsmeier reagent also finds application in the synthesis of large number of heterocyclic compounds.[5] Herein, we wish to report a facile route for the one-pot conversion of acyclic diacids to heterocyclic β-chlorovinyl aldehydes, under Vilsmeier conditions.

Scheme 1



1a-f **2a-f**

entry	**1**, **2**	X	R
1	**a**	NH	H
2	**b**	NH	CH_3
3	**c**	NH	Cl
4	**d**	NH	Br
5	**e**	O	H
6	**f**	S	H

A DMF solution of 2-[(carboxymethyl)amino]benzoic acid (**1a**) (5 mmol) was added dropwise with stirring at 0 °C to excess Vilsmeier reagent (6 equiv) previously prepared from DMF and $POCl_3$. The mixture was gradually allowed to attain rt and refluxed for further 6 h at 90 °C on a water bath and cooled and neutralized with crushed ice. The crude product was filtered and chromatographed (petroleum ether:ethyl acetate 80:20) to give 3-chloro-1*H*-indole-2-carboxaldehyde (**2a**) in 75% yield. The substituted 2-[(carboxymethyl)amino]benzoic acids **1b**−**d** also underwent the reaction smoothly (Scheme 1).

As vinyl chloride has been identified to be the intermediate leading to the formation of β-chlorovinyl aldehyde in a few cases,[6,1g] we pursued reaction conditions that would likely favor the formation of vinyl chloride group but prevent its subsequent formylation. But not even traces of vinyl chloride were isolated under mild conditions. Also when a methyl group was introduced on the carbon adjacent to the heteroatom of **2a**, **2b**, and **2c**, the cyclization reaction was completely prevented. Neither the formation of vinyl chloride nor that of β-chlorovinyl aldehyde could be detected by GC-MS analysis of the reaction mixture. When the reaction was performed on **1a** at rt using excess Vilsmeier reagent for

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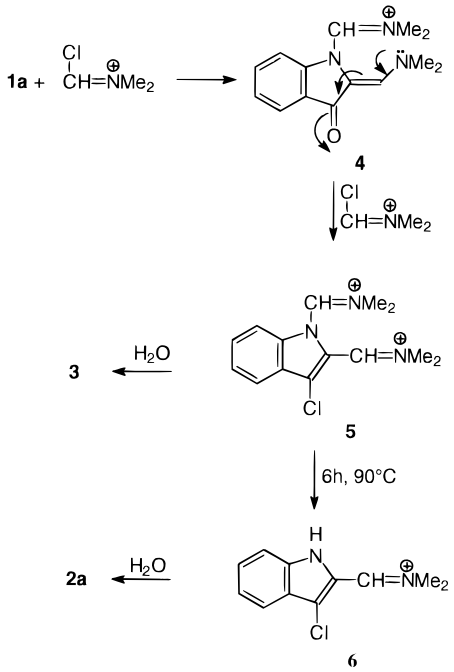
Table 1. Synthesis of β-Chlorovinyl Aldehydes from Diacids Using Vilsmeier Reagent

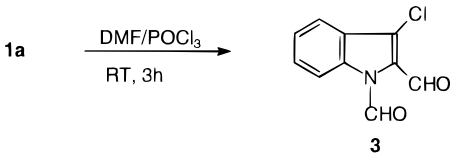
entry	product	method	mp, °C (lit.)	yield (%)
1	3-chloro-1*H*-indole-2-carboxaldehyde (**2a**)	A	172 (172−3)[11]	75
2	3-chloro-5-methyl-1*H*-indole-2-carboxaldehyde (**2b**)	B	175	45
3	3,5-dichloro-1*H*-indole-2-carboxaldehyde (**2c**)	A	192	70
4	5-bromo-3-chloro-1*H*-indole-2-carboxaldehyde (**2d**)	B	210	61
5	3-chlorobenzofuran-2-carboxaldehyde (**2e**)	A	73 (75)[9a]	21
6	3-chlorobenzo[*b*]thiophene-2-carboxaldehyde (**2f**)	A	103 (110)[9b]	51
7	3-chloroindole-1,2-dicarboxaldehyde (**3**)	A[a]	123	53
8	3-chloro-1*H*-pyrrole-2,4-dicarboxaldehyde (**8**)	B[b]	150	30

[a] Stirred for 1 h at rt and neutralized. [b] Crude product was extracted with $CHCl_3$ (3 × 50 mL).

Scheme 2

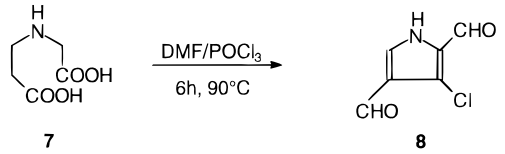


2 h, 3-chloroindole-1,2-dicarboxaldehyde (**3**) was obtained as the major product in 53% yield along with traces of **2a**. This indicates that **3** is a likely intermediate involved in the formation of **2a**.



Although it is premature to propose a detailed mechanism at this stage, based on the above results a plausible mechanism can be proposed (Scheme 2).[7] The formylation and decarboxylation of the dicarboxylic acid **1a** along with subsequent intramolecular cyclization gives the intermediate **4** which is then readily converted to the chloro derivative **5**. The hydrolysis of **5** yields the diformylated product **3**. However, under vigorous reaction conditions **5** is deformylated to **6** which on hydrolysis yields **2a**. The present study is the first of its kind where a carbonyl group is generated *in situ* under Vilsmeier conditions by the ortho-interactions of two COOH groups. The *in situ* generation of carbonyl group has an additional advantage in the synthesis of indole-2-carboxaldehydes. The previous syntheses of heterocyclic β-chlorovinyl aldehydes make use of the corresponding heterocyclic precursors as the starting material.[8] But indoxyls which are unsubstituted at nitrogen are unstable and rapidly undergo aerobic oxidative dimerization to indigo.[9] Therefore 3-chloro-1*H*-indole-2-carboxaldehydes were previously prepared[10] by the reaction of N-protected indoxyls followed by the removal of protecting group from the product. Since indoxyls are generated *in situ* in our reaction and are rapidly converted to the products, the need for handling unstable indoxyls is avoided.

In analogy to the synthesis of indole series, the reaction was successfully extended for the synthesis of other benzfused heterocycles such as 3-chlorobenzofuran-2-carboxaldehyde (**2e**) and 3-chlorobenzo[*b*]thiophene-2-carboxaldehyde (**2f**) (Scheme 1). When Vilsmeier−Haack reaction was performed on *N*-carboxymethyl β-alanine **7**, the only product that could be isolated was 3-chloro-1*H*-pyrrole-2,4-dicarboxaldehyde (**8**) in 30% yield. This implies that benzfusion is not an essential factor for the cyclization of diacids. The results are summarized in Table 1.



Experimental Section

Melting points were measured in capillary tubes and are uncorrected. Analytical thin layer chromatography was performed on precoated sheets of silica gel with 0.25 mm thickness containing PF 254 indicator (Merck, Darmstadt). Column chromatography was performed with silica gel (60−120 mesh; SD fine, Boisar).

N-Carboxymethyl β-alanine[11] was prepared following the literature procedure. 2-(Carboxymethoxy)benzoic acid and 2-[(carboxymethyl)thio]benzoic acid were prepared from salicylic acid and thiosalicylic acid, respectively, on treatment with an alkaline solution of chloroacetic acid. The substituted 2-[(carboxymethyl)amino]benzoic acids were prepared by the treatment of corresponding substituted anthranilic acids[12] with chloroacetic acid in alkaline medium.

Synthesis of Heterocyclic β-Chlorovinyl Aldehydes. General Procedure A. The Vilsmeier reagent was prepared

(7) Aldoketene is proposed to be the intermediate involved in the formation of vinamidinium salts from the Vilsmeier reaction of RCH_2-COOH. For the mechanism see Reichardt, C.; Hallbritter, K. *Leibigs. Ann. Chem.* **1970**, *737*, 99.

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by the dropwise addition of $POCl_3$ (2.8 mL, 30 mmol) to cooled DMF (5 mL) under constant stirring. The dicarboxylic acid (5 mmol) was dissolved in 5 mL of DMF and added dropwise to the Vilsmeier reagent. The reaction mixture was gradually allowed to attain rt, stirred for further 30 min, refluxed on a water bath maintained at 60−80 °C for 4−6 h. After the completion of the reaction, the reaction mixture was cooled and neutralized with crushed ice. The filtration and column chromatography of the crude product afforded the cyclized products in given yields.

General Procedure B. The dicarboxylic acid (5 mmol) was dissolved in 10 mL of DMF, and the solution was cooled to 0 °C. $POCl_3$ (2.8 mL, 30 mmol) was added dropwise with stirring over a period of 10 min. The reaction mixture was allowed to attain rt and refluxed for further 4−6 h at 80−90 °C. After the completion of the reaction, the reaction mixture was cooled and neutralized with saturated aq NaOAc solution. The crude product was filtered and chromatographed to afford the products in requisite yields.

3-Chloro-1*H*-indole-2-carboxaldehyde (2a). General procedure A was applied to 2-[(carboxymethyl)amino]benzoic acid **1a** (5 mmol, 0.975 g). The crude product was chromatographed (80:20 petroleum ether:ethyl acetate) to afford pale yellow needles of **2a** in 75% yield: mp 172 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.83 (br s, 1H), 10.05 (s, 1H), 7.68 (t, 1H, J = 4.1 Hz), 7.49 (d, 1H, J = 8.4 Hz), 7.37 (t, 1H, J = 7.7 Hz), 7.18 (t, 1H, J = 7.5 Hz); MS *m/e* (rel intensity) 179 (M^+, 100), 150 (23), 129 (29), 89 (25), 63 (12), 39 (5); IR (KBr) 1654, 2849, 3291 cm^{-1}. Anal. Calcd for C_9H_6ClNO: C, 60.18; H, 3.37; N, 7.80. Found: C, 60.54; H, 3.48; N, 8.06.

3-Chloro-5-methyl-1*H*-indole-2-carboxaldehyde (2b). General procedure B was applied to 2-[(carboxymethyl)amino]-5-methylbenzoic acid (**1b**) (5 mmol, 1.045 g). The crude product was chromatographed (40:60 petroleum ether:ethyl acetate) to afford red crystals of **2b** in 45% yield: mp 175 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.02 (s, 1H), 9.19 (br s, 1H), 7.50 (s, 1H), 7.32−7.23 (m, 2H), 2.46 (s, 3H, CH_3); MS *m/e* (rel intensity) 193 (M^+, 100), 164 (32), 158 (22), 137 (11), 128 (12), 102 (20), 77 (17), 51 (15), 39 (5); IR (KBr) 1661, 3281 cm^{-1}. Anal. Calcd for $C_{10}H_8ClNO$: C, 62.02; H, 4.17; N, 7.24. Found: C, 62.47; H, 4.24; N, 7.08.

3,5-Dichloro-1*H*-indole-2-carboxaldehyde (2c). General procedure A was applied to 5-chloro-2-[(carboxymethyl)amino]-benzoic acid (**1c**) (5 mmol, 1.145 g). The crude product was chromatographed (40:60 petroleum ether:ethyl acetate) to afford **2c** in 70% yield: mp 192 °C; ^{1}H NMR (300 MHz, DMSO) δ 12.34 (br s, 1H), 10.00 (s, 1H), 7.71 (s, 1H), 7.50−7.35 (m, 2H), MS *m/e* (rel intensity) 213 (M^+, 100), 184 (16), 157 (24), 150 (22), 123 (33), 114 (13), 87 (17), 73 (11), 40 (13); IR (KBr) 1662, 3281 cm^{-1}. Anal. Calcd for $C_9H_5Cl_2NO$: C, 50.50; H, 2.36; N, 6.55. Found: C, 50.82; H, 2.40; N, 6.43.

5-Bromo-3-chloro-1*H*-indole-2-carboxaldehyde (2d). General procedure B was applied to 5-bromo-3-chloro-2-[(carboxymethyl)amino]benzoic acid (**1d**) (5 mmol, 1.345 g). The crude product was chromatographed (20:80 petroleum ether:ethyl acetate) to afford **2d** in 61% yield: mp 210 °C; ^{1}H NMR (300 MHz, DMSO) δ 12.20 (br s, 1H), 9.99 (s, 1H), 7.68 (d, 1H, J = 8.2 Hz), 7.48−7.42 (m, 1H), 7.23 (d, 1H, J = 7.2 Hz); MS *m/e* (rel intensity) 259 (M^+, 100), 230 (12), 203 (12), 150 (19), 123 (13), 114 (13), 87 (11), 44 (63); IR (KBr) 3269, 1657 cm^{-1}. Anal. Calcd for $C_9H_5BrClNO$: C, 41.81; H, 1.95; N, 5.42. Found: C, 42.06; H, 2.06; N, 5.83.

3-Chlorobenzofuran-2-carboxaldehyde (2e). General procedure A was applied to 2-(carboxymethoxy)benzoic acid (**1e**) (5 mmol, 0.91 g) to afford **2e** in 21% yield: mp 73 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.04 (s, 1H), 6.93−6.80 (m, 4H); MS *m/e* (rel intensity) 180 (M^+, 100), 152 (15), 123 (37), 89 (71), 63 (23), 39 (11); IR (KBr) 1680 cm^{-1}. Anal. Calcd for $C_9H_5ClO_2$: C, 59.85; H, 2.80. Found: C, 60.03; H, 2.91.

3-Chlorobenzo[*b*]thiophene-2-carboxaldehyde (2f). General procedure A was applied to 2-[(carboxymethyl)thio]-benzoic acid (**1f**) (5 mmol, 1.06 g). The crude product was chromatographed (60:40 petroleum ether:ethyl acetate) to afford **2f** in 51% yield: mp 103 °C; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO) δ 10.35 (s, 1H), 8.04−7.51 (m, 1H), 7.89−7.87 (m, 1H), 7.62−7.51 (m, 2H); MS *m/e* (rel intensity) 196 (M^+, 100), 168 (24), 132 (16), 123 (14), 89 (22), 69 (8), 44 (19); IR (KBr) 1216, 1664 cm^{-1}. Anal. Calcd for C_9H_5ClOS: C, 54.97; H, 2.57. Found: C, 55.32; H, 2.78.

3-Chloroindole-1,2-dicarboxaldehyde (3). 2-[(Carboxymethyl)amino]benzoic acid (**1a**) (5 mmol, 0.975 g) dissolved in 6.5 mL of DMF was added dropwise to the cooled solution of previously prepared Vilsmeier reagent as in procedure A. The solution was gradually allowed to attain rt and stirred for further 1 h. The reaction mixture was neutralized by the addition of crushed ice. The crude product was chromatographed (80:20 petroleum ether:ethyl acetate) to afford yellow needles of **3** in 53% yield: mp 123 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.21 (s, 1H), 10.20 (s, 1H), 8.54 (d, 1H, J = 8.5 Hz), 7.78 (d, 1H, J = 8.0 Hz), 7.67−7.62 (m, 1H), 7.49−7.44 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.25, 160.62, 136.12, 131.75, 130.34, 129.28, 126.24, 125.74, 120.64, 117.55; MS *m/e* (rel intensity) 207 (M^+, 9), 179 (100), 150 (18), 123 (28), 89 (48), 63 (22), 39 (17); IR (KBr) 1675, 1723 cm^{-1}. Anal. Calcd for $C_{10}H_6ClNO_2$: C, 57.88; H, 2.92; N, 6.75. Found: C, 58.13; H, 3.06; N, 6.46.

3-Chloro-1*H*-pyrrole-2,4-dicarboxaldehyde (8). General procedure B was applied to *N*-(carboxymethyl) β-alanine (**7**) (5 mmol, 0.735 g). The crude product was extracted with $CHCl_3$ (3 × 50 mL), organic layer was washed with brine and dried over Na_2SO_4, and solvent was evaporated and column chromatographed (20:80 petroleum ether:ethyl acetate) to afford **8** in 30% yield: mp 150 °C; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO) δ 12.45 (br s, 1H), 9.31 (s, 1H), 9.18 (s, 1H), 7.10 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO) δ 183.48, 177.45, 130.31, 128.82, 122.40; MS *m/e* (rel intensity) 156 (M^+, 100), 128 (20), 100 (62), 73 (60), 37 (51); IR (KBr) 3248, 1663 cm^{-1}. Anal. Calcd for $C_6H_4ClNO_2$: C, 45.73; H, 2.56; N, 8.89. Found: C, 46.07; H, 2.87; N, 8.63.

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