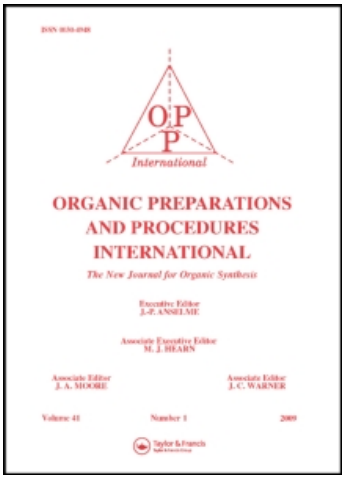


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

A Practical and Efficient Vilsmeier Synthesis of 3-Chloroindole-2-carboxaldehydes

Z. H. Li[a]; Z. R. Hu[a]; R. E. Chen[a]; W. K. Su[a]
[a] Key Laboratory of Pharmaceutical Engineering of Ministry of Education, College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou, P. R. China

Online publication date: 01 October 2010

To cite this Article Li, Z. H. , Hu, Z. R. , Chen, R. E. and Su, W. K.(2010) 'A Practical and Efficient Vilsmeier Synthesis of 3-Chloroindole-2-carboxaldehydes', Organic Preparations and Procedures International, 42: 5, 479 — 484
To link to this Article: DOI: 10.1080/00304948.2010.514793
URL: http://dx.doi.org/10.1080/00304948.2010.514793

Organic Preparations and Procedures International, 42:479–484, 2010

ISSN: 0030-4948 print
DOI: 10.1080/00304948.2010.514793

OPPI BRIEFS

A Practical and Efficient Vilsmeier Synthesis of 3-Chloroindole-2-carboxaldehydes

Z. H. Li, Z. R. Hu, R. E. Chen, and W. K. Su

Key Laboratory of Pharmaceutical Engineering of Ministry of Education, College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou, P. R. China

The indole ring is regarded as a priviledged structural moiety in many naturally occurring alkaloids[1] or synthetic drugs.[2] In particular, 3-chloroindole-2-carboxaldehyde derivatives display important pharmacological properties such as anti-HIV[3], antitumor[4] and anticancer activities.[5] Recently, some important papers have been published on the synthesis and functionalization of indoles.[6–8] Although the Vilsmeier cyclization of 2-[(carboxymethyl)amino]benzoic acids **1** has provided an effective and more convenient approach for the construction of indole derivatives without any metal catalysts, it suffers the disadvantages of low efficiency with some substrates and unsatisfactory yields.[9] Herein, we disclose an efficient and practical process for the improved synthesis of 3-chloroindole-2-carboxaldehydes **2** from readily accessible 2-[(carboxymethyl)amino]benzoic acids **1** (*Scheme 1*).

Initially, 2-[(carboxymethyl)amino]benzoic acid (**1a**) was used as a representative substrate to examine the best reaction conditions. Treatment of **1a** with the Vilsmeier reagent (6.0 equiv.) prepared from DMF and *bis*-(trichloromethyl) carbonate (BTC) at 75°C proceeded smoothly in 1,2-dichloroethane as indicated by TLC and furnished only one product after work-up and purification by column chromatography. The product was characterized as 3-chloroindole-2-carboxaldehyde (**2a**, *Scheme 1*) by its ^{1}H NMR, ^{13}C NMR and MS data. Based on our previous studies[10] and encouraged by these results, the reaction conditions including solvent, temperature and the ratio of **1a** to DMF/BTC were investigated. In order to avoid the use of 1,2-dichloroethane, much effort was made to select a suitable solvent. To our delight, it was found that 2-methyltetrahydrofuran (2-MeTHF) was the better choice than 1,2-dichloroethane, toluene, CH_3CN and THF. As an eco-friendly

Submitted December 4, 2009.
Address correspondence to W. K. Su, Key Laboratory of Pharmaceutical Engineering of Ministry of Education, College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou 310014, P. R. China. E-mail: pharmlab@zjut.edu.cn

a) $R^1 = R^2 = R^3 = R^4 = H$; b) $R^1 = R^3 = R^4 = H$, $R^2 = Cl$; c) $R^1 = R^3 = R^4 = H$, $R^2 = Br$; d) $R^1 = R^3 = R^4 = H$, $R^2 = CH_3$; e) $R^1 = R^2 = R^3 = H$, $R^4 = Cl$; f) $R^1 = R^3 = R^4 = H$, $R^2 = NO_2$; g) $R^1 = R^3 = H$, $R^2 = R^4 = Br$; h) $R^1 = R^3 = H$, $R^2 = R^4 = CH_3$; i) $R^1 = R^3 = H$, $R^2 = CH_3$, $R^4 = Br$; j) $R^1 = R^2 = R^4 = H$, $R^3 = F$; k) $R^1 = R^4 = H$, $R^2 = R^3 = Cl$; l) $R^1 = R^2 = Cl$, $R^3 = R^4 = H$

Scheme 1

solvent, 2-MeTHF derived from renewable sources can be efficiently recovered according to a known procedure[11] and the reaction afforded in high yields. A series of experiments revealed that the optimal results were obtained when the reaction of **1a** was performed with 5.0 equiv. of BTC/DMF in 2-MeTHF at 80°C for 4 h, whereby the reaction afforded **2a** exclusively in 84% yield (*Table 1*).

To explore the effect of the substituents on the phenyl ring in the reaction of 2-[(carboxymethyl)amino]benzoic acids **1** with BTC/DMF, a series of substrates with diverse electronic properties were then investigated. As illustrated in *Table 1*, various 3-chloroindole-2-carboxaldehydes **2** were obtained from the corresponding 2-[(carboxymethyl)amino]benzoic acids **1**. Generally, the results demonstrated that the reactivity of substrates with an electron-withdrawing group (especially at the 5,7-position) is much higher than those with an electron-donating substituent. The structures of the known compounds were confirmed by comparison of their mps. with literature mps. and spectral data (IR, 1H-NMR). The new products were fully characterized by IR, mass spectra, 1H-NMR, ^{13}C NMR (*Table 2*) and elemental analysis (*Table 3*).

Based on these results and a previous report,[9] a plausible mechanism can be proposed (*Scheme 2*). First, the cyclization of the dicarboxylic acid **1a** promoted by one equiv. of halomethyleniminium salt gave intermediate **B**. This is followed by the formylation of **B** to provide adduct **C**, which then undergoes intramolecular attack along with elimination of carbon dioxide to afford intermediate **E**. **F** was then readily formed by chlorination of **E**.

In summary, a highly efficient and practical method for the synthesis of the substituted 3-chloroindole-2-carboxaldehydes in an eco-friendly solvent has been developed. Studies on the extension of this protocol are currently on-going in our laboratories.

Experimental Section

2-[(Carboxymethyl)amino]benzoic acid (**1a**) was prepared using the literature procedure.[12] The substituted 2-[(carboxymethyl)amino]benzoic acids (except **1f**) were prepared by the treatment of corresponding substituted anthranilic acids with chloroacetic acid in alkaline medium.[13] Substituted anthranilic acids were prepared from substituted

Table 1
Synthesis of Indoles **2a–l** using BTC /DMF

Product[a]	Yield (%)	Time (h)	mp (°C) (*lit*. mp)	IR (cm^{-1})	^1H NMR (δ)
2a	84	4	171–172 (172[9])	1653 3290 3443	^1H NMR ($CDCl_3$) δ: 10.06 (s, 1 H, CHO), 9.05 (br s, 1 H, NH), 7.75–7.77 (m, 1 H, PhH), 7.41–7.47 (m, 2 H, PhH), 7.23–7.27 (m, 1 H, PhH)
2b[b]	88	3	192–193 (193[9])	1654 3280 3415	^1H NMR (DMSO–d_6) δ: 12.49 (br s, 1 H, NH), 10.01 (s, 1 H, CHO), 7.74 (s, 1 H, PhH), 7.51 (d, 1 H, $J = 8.8$ Hz, PhH), 7.43 (dd, 1 H, $J_1 = 2.0$ Hz, $J_2 = 8.8$ Hz, PhH)
2c	86	3	208–209 (210[9])	1653 3265 3452	^1H NMR (DMSO-d_6) δ: 12.51 (br s, 1 H, NH), 10.01 (s, 1 H, CHO), 7.88 (d, 1 H, $J = 1.6$ Hz, PhH), 7.56 (dd, 1 H, $J_1 = 2.0$ Hz, $J_2 = 8.8$ Hz, PhH), 7.45 (d, 1 H, $J = 8.8$ Hz, PhH)
2d	82	4	175–176 (175[9])	1646 3287 3454	^1H NMR ($CDCl_3$) δ: 10.03 (s, 1 H, CHO), 8.98 (br s, 1 H, NH), 7.52 (s, 1 H, PhH), 7.31 (d, 1 H, $J = 8.4$ Hz, PhH), 7.27 (d, 1 H, $J = 7.2$ Hz, PhH), 2.47 (s, 3 H, CH_3)
2e[b]	87	3	168–169	1676 3299 3448	^1H NMR ($CDCl_3$) δ: 10.08 (s, 1 H, CHO), 9.04 (br s, 1 H, NH), 7.66–7.69 (m, 1 H, PhH), 7.45 (dd, 1 H, $J_1 = 0.8$ Hz, $J_2 = 7.6$ Hz, PhH), 7.17–7.25 (m, 1 H, PhH)
2f	92	3	242–245	1654 3263 3448	^1H NMR (DMSO-d_6) δ: 12.96 (br s, 1 H, NH), 10.07 (s, 1 H, CHO), 8.59 (s, 1 H, PhH), 8.24 (d, 1 H, $J = 9.2$ Hz, PhH), 7.65 (d, 1 H, $J = 9.2$ Hz, PhH)
2g[b]	90	3	232–234	1636 3453	^1H NMR (400 MHz, DMSO-d_6) δ: 12.81 (br s, 1 H, NH), 10.06 (s, 1 H, CHO), 7.90 (s, 1 H, PhH), 7.86 (s, 1 H, PhH)
2h	80	5	202–203	1667 3319 3451	^1H NMR ($CDCl_3$) δ: 10.02 (s, 1 H, CHO), 8.87 (br s, 1 H, NH), 7.36 (s, 1 H, PhH), 7.07 (s, 1 H, PhH), 2.46 (t, 6 H, 2 CH_3)
2i[b]	85	4	216–217	1657 3302 3455	^1H NMR ($CDCl_3$) δ: 10.05 (s, 1 H, CHO), 8.88 (br s, 1 H, NH), 7.47 (s, 1 H, PhH), 7.45 (s, 1 H, PhH), 2.46 (s, 3 H, CH_3)
2j	88	3	196–198	1656 3280 3442	^1H NMR ($CDCl_3$) δ: 10.00 (s, 1 H, CHO), 9.37 (br s, 1 H, NH), 7.71 (dd, 1 H, $J_1 = 5.2$ Hz, $J_2 = 8.8$ Hz, PhH), 7.00–7.14 (m, 2 H, PhH)

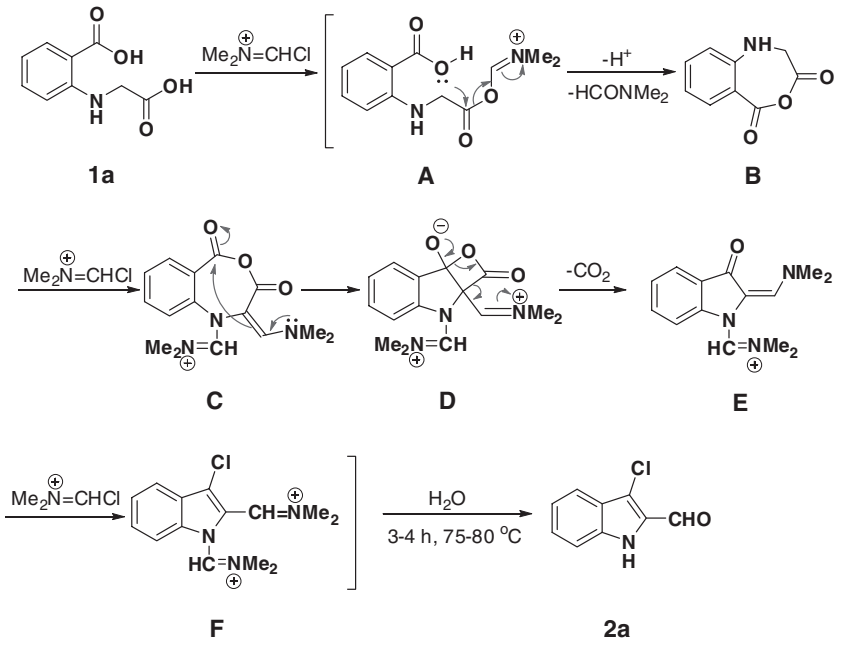
(Continued on next page)

Table 1
Synthesis of Indoles **2a–l** using BTC/DMF *(Continued)*

Product[a]	Yield (%)	Time (h)	mp (°C) (*lit*. mp)	IR (cm^{-1})	^{1}H NMR (δ)
2k	91	3	252–253	1654 3290 3445	^{1}H NMR (DMSO-d_6) δ: 12.59 (br s, 1 H, NH), 10.01 (s, 1 H, CHO), 7.98 (s, 1 H, PhH), 7.69 (s, 1 H, PhH)
2l	89	3	248–249	1654 3290 3445	^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.81 (br s, 1 H, NH), 10.03 (s, 1 H, CHO), 7.56 (d, 1H, J = 8.8 Hz, PhH), 7.46 (d, 1 H, J = 8.8 Hz, PhH)

a) Yellow solids unless otherwise stated. b) Red solid.

anilines.[14–16] 2-(Carboxymethylamino)-5-nitrobenzoic acid (**1f**) was prepared from 2-chloro-4-nitrobenzoic acid.[17] ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 400 MHz instrument in $CDCl_3$ or DMSO-d_6 as the solvent, and chemical shifts are expressed in δ using TMS as internal standard. Mass spectra were measured on a Trace Finnigan DSQ. Elemental analyses were performed on a VarioEL-3 instrument. Infrared spectra were determined on a Thermo Nicolet Avatar 370 spectrophotometer. Melting points were obtained on a capillary melting point apparatus and are uncorrected.



Scheme 2

Table 2
^{13}C NMR and Mass Spectra for Compounds **2e-l**

Product	^{13}C NMR	MS (EI)
2e	^{13}C NMR ($CDCl_3$): 179.9, 133.5, 130.7, 127.3, 126.7, 122.4, 119.2, 118.1, 117.8	m/z (%) = 213 (100), 184 (18), 157 (12), 123 (11), 114 (14), 87 (6)
2f	^{13}C NMR (DMSO-d_6): 180.9, 142.2, 138.8, 133.3, 123.7, 121.9, 117.0, 116.0, 114.6	m/z (%) = 224 (100), 194 (13), 178 (30), 168 (4), 123 (21), 114 (22), 87 (8)
2g	^{13}C NMR (DMSO-d_6): 181.1, 133.8, 132.1, 131.8, 127.0, 121.2, 113.6, 112.6, 107.2	m/z (%) = 337 (100), 308 (81), 281 (6), 230 (5)
2h	^{13}C NMR ($CDCl_3$): 180.0, 134.7, 131.7, 130.9, 130.1, 125.4, 121.7, 117.1, 21.4, 16.2	m/z (%) = 207 (100), 192 (34), 178 (18), 115 (10)
2i	^{13}C NMR ($CDCl_3$): 179.7, 133.4, 132.9, 132.3, 130.7, 126.5, 119.0, 117.2, 105.5, 21.2	m/z (%) = 273 (100), 244 (5), 192 (38), 164 (11), 128 (12)
2j	^{13}C NMR ($CDCl_3$): 179.6, 164.6, 162.2, 122.3, 122.2, 112.1, 111.8, 98.7, 98.5	m/z (%) = 197 (100), 168 (24), 141 (15), 132 (11), 84 (15)
2k	^{13}C NMR (DMSO-d_6): 180.6, 134.9, 132.1, 129.9, 124.5, 124.1, 120.8, 114.9, 113.2	m/z (%) = 247 (100), 218 (13), 184 (22), 157 (17), 148 (9), 121 (6)
2l	^{13}C NMR (DMSO-d_6): 181.0, 136.0, 132.3, 128.5, 125.0, 123.5, 121.3, 114.1, 113.0	m/z (%) = 247 (100), 220 (18), 184 (20), 157 (15), 148 (12), 121 (4)

Table 3
Elemental Analysis for Compounds **2e-l**

	Elemental Analysis Found (Calcd)		
Cmpd **2**	C	H	N
2e	50.42 (50.50)	2.39 (2.35)	6.49 (6.54)
2f	48.06 (48.13)	2.28 (2.24)	12.44 (12.47)
2g	32.11 (32.04)	1.14 (1.19)	4.09 (4.15)
2h	63.58 (63.62)	4.91 (4.85)	6.69 (6.75)
2i	44.03 (44.07)	2.55 (2.59)	5.18 (5.14)
2j	54.66 (54.71)	2.50 (2.55)	7.14 (7.09)
2k	43.56 (43.50)	1.69 (1.62)	5.58 (5.64)
2l	43.52 (43.50)	1.67 (1.62)	5.59 (5.64)

Typical Procedure for the Preparation of 3-Chloroindole-2-carboxaldehydes

The Vilsmeier reagent was prepared by adding a solution of BTC (2.97 g, 10 mmol) in 2-MeTHF (10 mL) to a solution of DMF (3 mL, 30 mmol) in 2-MeTHF (25 mL) immersed in an ice-water bath under constant stirring, then the ice-water bath was removed. The temperature was raised to 25°C and was stirred for an additional 20 min, followed by the addition of 2-[(carboxymethyl)amino]benzoic acid (**1a**, 6 mmol) to the Vilsmeier reagent. The reaction mixture was maintained at 25°C and stirred for further 20 min, then heated to reflux for 4 h at 80°C. After completion of the reaction, the reaction mixture was cooled and poured into ice-water and was extracted by 2-MeTHF (3 × 30 mL). The combined organic phase was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered and the solvent was recovered under reduced pressure. The crude product was purified by flash silica gel chromatography (petroleum ether/ethyl acetate 4:1 v/v) to give pure **2a** as a yellow solid.

Acknowledgement

We are grateful to National Key Technology R&D Program 2007BAI34B00 and the Natural Science Foundation of Zhejiang province (No. 202095) and the Natural Science Foundation of China (No. 20876147) and the Opening Foundation of Zhejing Provincial Top Key Pharmaceutical Discipline for financial help.

References

1. H. Ishikawa, D. A. Colby, S. Seto, P. Va and D. L. Boger, *J. Am. Chem. Soc.*, **131**, 13 (2009).
2. K. Eva-Maria, L. Susann and P. Carlo, *J. Med. Chem.*, **52**, 3474 (2009).
3. Z. Q. Wang and R. Vince, *Bioorg. Med. Chem.*, **16**, 3587 (2008).
4. G. Lena, J. A. Trapani and V. R. Sutton, *J. Med. Chem.*, **51**, 23 (2008).
5. I. Yavari, M. Adib and M. H. Sayahi, *J. Chem. Soc. Perkin 1*, 1517 (**2002**).
6. D. Karin, R. Thomas and S. Troels, *Org. Lett.*, **11**, 221 (2009).
7. O. Yusuke, C. Hiroaki and O. Shinya, *J. Org. Chem.*, **74**, 18 (2009).
8. M. V. DeBenedetto, M. E. Green and S. Y. Wan, *Org. Lett.*, **11**, 835 (2009).
9. V. J. Majo and P. T. Perumal, *J. Org. Chem.*, **61**, 6523 (1996).
10. W. K. Su, X. Y. Zhu and Z. H. Li, *Org. Prep. Proced. Int.*, **41**, 69 (2009).
11. W. H. Zhong, Y. T. Wu and X. X. Zhang, *J. Chem. Res.*, 370 (**2009**).
12. L. L. McKinney, E. A. Setzkorn and E. H. Uhing, *J. Am. Chem. Soc.*, **74**, 1942 (1952).
13. G. E. Dunn and R. Prysiazniuk, *Can. J. Chem.*, **39**, 285 (1961).
14. A. Zabeer, A. Bhagat and O. P. Gupta, *Eur. J. Med. Chem.*, **41**, 429 (2006).
15. M. R. Pavia, W. H. Moos and F. M. Hershenson, *J. Org. Chem.*, **55**, 560 (1990).
16. Y. Nagao, M. Yagi and T. Iketa, *Tetrahedron Lett.*, **23**, 201 (1982).
17. M. L. Docampo, P. E. Rolando, E. B. Ana and G. R. Angel, *Eur. J. Org. Chem.*, 411 (**2007**).