Pergamon

Tetrahedron Letters 43 (2002) 5793–5795

TETRAHEDRON LETTERS

Friedel–Crafts acylation of indoles in acidic imidazolium chloroaluminate ionic liquid at room temperature

Kap-Sun Yeung,* Michelle E. Farkas, Zhilei Qiu and Zhong Yang

Bristol-Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway, PO Box 5100, Wallingford, CT 06492, USA

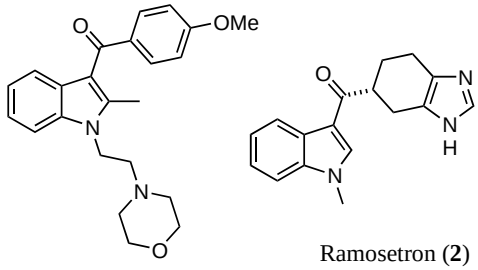
Received 29 May 2002; revised 15 June 2002; accepted 18 June 2002

Abstract—A practical and convenient protocol has been developed for the acidic 1-ethyl-3-methylimidazolium chloroaluminate ionic liquid (generated from 1-ethyl-3-methylimidazolium chloride (EmimCl) and aluminium chloride ($X(AlCl_3)$, mole fraction $X=0.67$–0.75) promoted Friedel–Crafts acylation of indoles at room temperature. The simple experimental procedure provides 3-substituted indoles in good to high yields with less electron rich indole ring systems.

Substituted indoles are drug fragments commonly found in molecules of pharmaceutical interest in a variety of therapeutic areas.[1] Interesting examples include the analgesic, Pravodoline (**1**), and the antiemetic, Ramosetron (**2**) (Fig. 1).

In our laboratories, we were interested in the synthesis of drug-like molecules that contained substituted indoles and which were most accessible via an acylation at the C_3 position of *N*-unprotected indoles as the pivotal step. The sporadic efficiency of standard methods we encountered in our reactions led us to become intrigued by the possibility of applying the strongly acidic imidazolium chloroaluminate ionic liquid[2] generated from 1-ethyl-3-methylimidazolium chloride (EmimCl) and aluminum chloride ($X(AlCl_3)$, mole fraction X[2a,3] $=0.67$–0.75, Fig. 2) to promote the Friedel–Crafts[3,4] type acylation on *N*-unprotected indoles.[4a] The use of imidazolium chloroaluminate in organic synthesis represents an underexplored area. To date, examples of useful and practical reactions mediated by EmimCl-$X(AlCl_3)$ that can be conveniently carried out on laboratory scale are still rare.[2]

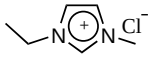
We explored representative examples (Table 1) of the acidic imidazolium chloroaluminate-promoted acylation reaction (Scheme 1) of substituted *N*-unprotected indoles with acid chlorides. Good to high yields were obtained[5a] and no side products of over acylation observed. Useful and diverse functional groups, e.g. halogens, carbonyl, anisole, furan, CN and NO_2, were well tolerated under these strongly acidic conditions. The regiochemistry was confirmed by correlation with known products (**3**[6a] and **11**[6c]).[5b]



Pravadoline (**1**) Ramosetron (**2**)

Figure 1.

To the best of our knowledge, the preparation of products **4** to **10** has not been reported in the literature before. These conditions frequently offer advantages over existing methods. For example, 3-acetyl-4-nitroindole (**3**), a useful intermediate for the synthesis of indole alkaloid natural products,[6a] was previously synthesized only by non-regioselective nitration of 3-acetylindole in poor yields (2%,[6b] 20%[6a]). The use of poisonous carbon disulfide and excessive $AlCl_3$ can also



EmimCl X = 0.67-0.75

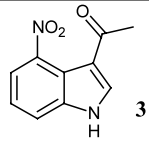
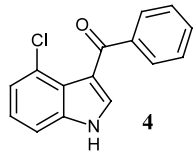
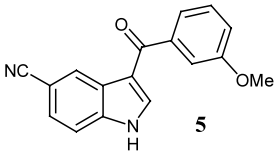
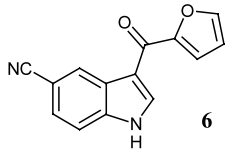
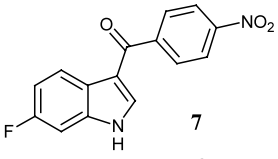
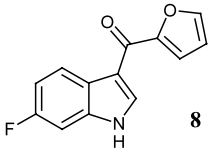
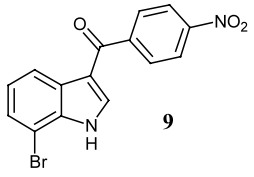
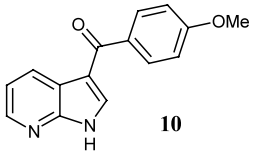
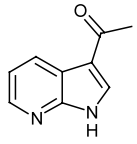
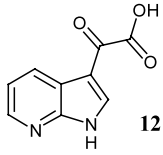
Figure 2.

Keywords: indole; acylation; imidazolium chloroaluminate; ionic liquid.

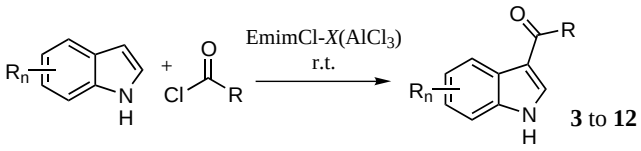
* Corresponding author. Fax: +1 203 677 7072; e-mail: kapsun.yeung@bms.com

0040-4039/02/$ - see front matter
PII: S0040-4039(02)01185-1

Table 1. Examples of products and their yields obtained from the EimCl-$X(AlCl_3)$ promoted acylation of indoles

Entry	Product	Yield (%)[5a]
1	 **3**	87
2	 **4**	71
3	 **5**	78
4	 **6**	75
5	 **7**	66
6	 **8**	59
7	 **9**	55
8	 **10**	79
9	 **11**	57
10	 **12**	38[a]

[a]Ethyl chlorooxoacetate was used; unoptimized yield.

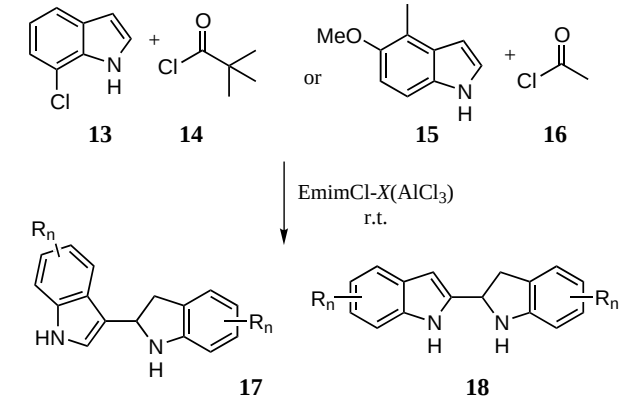


Scheme 1.

be avoided in the preparation of 3-acetyl-7-azaindole (**11**).[6c] The products, including the very polar glyoxylic acid derivative **12**, usually precipitated in high purity from the reaction mixture after the aqueous quench. Compound **12** was prepared using ethyl chlorooxoacetate as the acylating agent and was directly isolated as the acid from the reaction mixture. The formation of the ester was observed by LC/MS, but this was converted to the acid on extended reaction time. It has not been determined if the ester hydrolysis is due to the strongly acidic medium itself, or a result of adventitious moisture present in the reaction mixture[2a] or a combination of both. In practice, this is useful if subsequent ester hydrolysis is required for synthesis.[7] A minimum of 2 equiv. of EimCl was required to provide sufficient volume to take up the starting material for a reaction conducted on a reasonable scale,[8] although we believed that equimolar amount of [EimCl-$X(AlCl_3)$] sufficed to promote the reaction.

For reactions of relatively less reactive acid chlorides, e.g. pivaloyl chloride **14** (Scheme 2), or electron rich indoles, e.g. **15**, Mannich-type indole dimerization[9] was the predominant reaction pathway that gave rise to a mixture of the dimeric isomers **17** and **18** in different ratios.[10]

A general experimental procedure is as follows:[11] To EimCl (2 equiv.; purchased from TCI; weighed under a stream of nitrogen) stirred in an oven-dried round bottom flask at ambient temperature under a nitrogen atmosphere, was added $AlCl_3$ (4 equiv., $X=0.67$; weighed under a stream of nitrogen). Anhydrous powder of $AlCl_3$ packaged under argon in ampules (purchased from Aldrich) was preferred. For more electron deficient indole ring systems, 6 equiv. of $AlCl_3$ ($X=0.75$) would be necessary. The mixture was vigorously stirred to form a liquid. After all the heat generated from mixing was dissipated, indole (1 equiv.) was added



Scheme 2.

to the ionic liquid and the reaction mixture stirred until a homogenous mixture resulted. Acid chloride (2 equiv.) was added and the reaction mixture stirred at ambient temperature.[12] The progress of the reaction was monitored by TLC or LC/MS, and typical reaction times were 1 to 18 h. After completion, the mixture was cooled in an ice-water bath and the reaction mixture quenched by carefully adding excess ice water. The precipitates formed were filtered and washed with water. Alternatively, after quenching, the mixture was extracted with an organic solvent and the extracts evaporated in vacuo. Crude product of lesser purity was further purified by chromatography or recrystallization.

In summary, a practical and convenient protocol has been developed for the Friedel–Crafts-type acylation of the C_3 position of indoles that is promoted by acidic imidazolium chloroaluminate ionic liquid at room temperature. This reaction appears to be much general for less electron rich indole ring systems. It can be applied to the synthesis of multiple-point pharmacophores of indoles substituted at different positions with versatile functionalities (e.g. Br, CN, NO_2, CO_2H, C=O, enolizable α-protons, anisole and furan), which can lead to unlimited chemical diversity.

Acknowledgements

We thank Dr. Nicholas A. Meanwell and Dr. John F. Kadow for valuable comments on the manuscript, and Dr. Alicia Regueiro-Ren for interesting discussions.

References

1. USP Dictionary, 2001 edition.
2. For general reviews on ionic liquids, see: (a) Welton, T. *Chem. Rev*. **1999**, *99*, 2071; (b) Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed*. **2000**, *39*, 3772; (c) Sheldon, R. *Chem. Commun*. **2001**, 2399; (d) various chloroaluminate species ($AlCl_4^-$, $Al_2Cl_7^-$, $Al_3Cl_{10}^-$) are present in the acidic ionic liquid, see (a) for details.
3. Boon, J. A.; Levisky, J. A.; Pflug, J. L.; Wilkes, J. S. *J. Org. Chem*. **1986**, *51*, 480.
4. (a) An example of Friedel–Crafts acylation of *N*,C_2-dialkyl-substituted indole using [EimCl-*X*$AlCl_3$] has been reported: Earle, M. J.; McCormac, P. B.; Seddon, K. R. *Green Chem*. **2000**, *2*, 261. For other Friedel–Crafts reactions using [EimCl-*X*$AlCl_3$], see: (b) Surette, J. K. D.; Green, L.; Singer, R. D. *Chem. Commun*. **1996**, *27*, 53; (c) Adams, C. J.; Earle, M. J.; Roberts, G.; Seddon, K. R. *Chem. Commun*. **1998**, 2097; (d) R. Y. Saleh, WO 0015594, 2000.
5. (a) Products were analytically pure and their yields obtained after purification by column chromatography or recrystallization. Further purification of products **3** and **11** was not required; (b) **product 3** ^{1}H NMR: (acetone-d_6) δ 11.52 (b s, 1H), 8.43 (d, $J=3.1$, 1H,), 7.85 (dd, $J=8.1$, 0.6, 1H), 7.60 (dd, $J=7.7$, 0.6, 1H), 7.42 (appeared as t, $J=7.9$, 1H), 2.48 (s, 3H); **product 11** ^{1}H NMR: (DMSO-d_6) δ 12.45 (b s, 1H), 8.459 (d overlapping with dd, $J=3.1$, 1H), 8.458 (dd, $J=7.9$, 1.6, 1H), 8.31 (dd, $J=4.7$, 1.6, 1H), 7.23 (dd, $J=7.9$, 4.7, 1H), 2.46 (s, 3H).
6. (a) Murase, M.; Koike, T.; Moriya, Y.; Tobinaga, S. *Chem. Pharm. Bull*. **1987**, *35*, 2656; (b) Noland, W. E.; Rush, K. R. *J. Org. Chem*. **1966**, *31*, 70; (c) Galvez, C.; Viladoms, P. *J. Heterocyclic Chem*. **1982**, *19*, 665.
7. The application of this one-pot acylation/ester hydrolysis procedure in synthesis will be reported in due time.
8. Typical reaction scale was about 2–4 mmol of indole, and the largest scale performed was about 45 mmol ($\sim$10 g) of indole.
9. For related dimerization of 3-substituted indoles induced by protic acids, see: (a) Smith, G. F.; Walters, A. E. *J. Chem. Soc*. **1961**, 940; (b) Hashizume, K.; Shimonishi, Y. *Bull. Chem. Soc. Jpn*. **1981**, *54*, 3806; (c) it is known that acylation of indoles using strong Lewis acids can sometimes be complicated by undesirable oligomerization: Okauchi, T.; Itonaga, M.; Minami, T.; Owa, T.; Kitoh, K.; Yoshino, H. *Org. Lett*. **2000**, *2*, 1485 and (d) Ottoni, O.; Neder, A. de V. F.; Dias, A. K. B.; Cruz, R. P. A.; Aquino, L. B. *Org. Lett*. **2001**, *3*, 1005.
10. The dimeric structure was supported by NMR and MS studies. The imidazolium chloroaluminate-promoted indole dimerization will be the subject of further investigations.
11. $AlCl_3$, EimCl and all reagents were used as received from commercial sources. The use of a glove box was not necessary.
12. The reaction mixture often became very viscous after all the reagents were well mixed.