Tetrahedron Letters 49 (2008) 6250–6253

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An efficient one-pot synthesis of 3-glyoxylic acids of electron-deficient substituted azaindoles by ionic liquid imidazolium chloroaluminate-promoted Friedel–Crafts acylation

Kap-Sun Yeung *, Zhilei Qiu, Michelle E. Farkas, Qiufen Xue, Alicia Regueiro-Ren, Zhong Yang, John A. Bender, Andrew C. Good, John F. Kadow

Bristol-Myers Squibb R&D, 5 Research Parkway, PO Box 5100, Wallingford, CT 06492, USA

ARTICLE INFO

Article history:
Received 19 July 2008
Revised 8 August 2008
Accepted 11 August 2008
Available online 15 August 2008

Keywords:
Friedel–Crafts acylation
Ionic liquid
Imidazolium chloroaluminate
Electron-deficient azaindoles
Azaindole-3-glyoxylic acid

ABSTRACT

An efficient, one-pot Friedel–Crafts acylation/hydrolysis reaction promoted by the acidic ionic liquid 1-ethyl-3-methylimidazolium chloroaluminate (generated from 1-ethyl-3-methylimidazolium chloride (EmimCl) and aluminum chloride ($X(AlCl_3)$, mole fraction $X = 0.75$) for the formation of 3-glyoxylic acid derivatives of electron-deficient, substituted 4- and 6-azaindoles is described.

An early step in the entry of HIV into host cells is the attachment of the viral envelope glycoprotein gp120 to the host cell receptor CD4. During the course of a drug discovery program to identify new anti-HIV agents, it was discovered that this step can be inhibited by a class of indole- or azaindole-oxoacetic piperazinyl benzamides that appear to act by stabilizing a conformation of viral gp120 that is not recognized by the host cell receptor CD4.[1] Azaindole inhibitors BMS-378806 and BMS-488043 (Fig. 1) progressed into clinical studies with the latter compound providing proof-of-concept for this inhibitory mechanism in HIV-infected patients.[1]

Further drug discovery efforts in this area required the synthesis of azaindole-3-glyoxylates, the core structural element found in BMS-378806 and BMS-488043. Methodology that would allow the direct Friedel–Crafts acylation of azaindoles (e.g., substituted 4- and 6-azaindoles **1**–**5** as shown in Fig. 2) with methyl or ethyl chlorooxoacetate was considered to be the most efficient approach.

However, acylation of **1**–**5** with methyl or ethyl chlorooxoacetate under established protocols suitable for unsubstituted azaindoles[2] were unsatisfactory, providing poor yields of products. For example, the use of a substantial excess of $AlCl_3$ (20 equiv) in

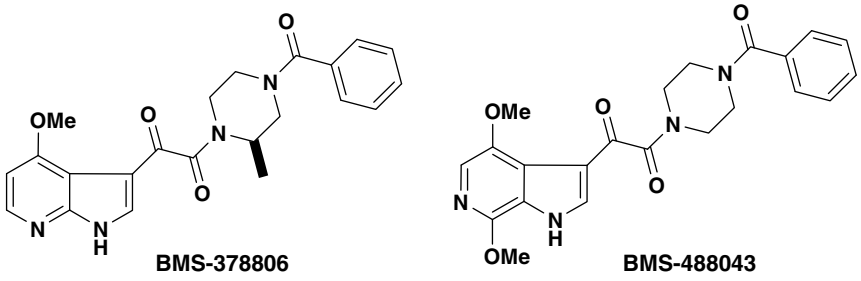


Figure 1.

* Corresponding author. Tel.: +1 203 677 6897; fax: +1 203 677 7702.
E-mail address: kapsun.yeung@bms.com (K.-S. Yeung).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.08.045

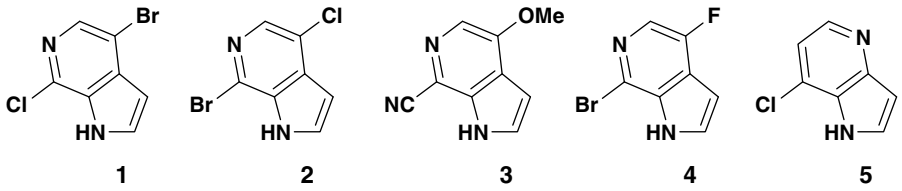


Figure 2.

CH_2Cl_2 at room temperature was necessary for the acylation reaction of 6-azaindoles **1** and **2** to proceed. A total of 40 equiv of $AlCl_3$ and 40 equiv of methyl chlorooxoacetate were ultimately required for the completion of this reaction, but still provided only poor yields of the products. The use of these conditions also exacerbated the practical difficulties of isolating the product from the reaction mixture. Major decomposition occurred when 7-cyano-4-methoxy-6-azaindole (**3**) was used in these conditions. Although a maximum of 15% yield was obtained when nitromethane was used as a co-solvent (10% in CH_2Cl_2), a minimum of 10 equiv of $AlCl_3$ were still required to acylate azaindole **3**. For the acylation of **4** and **5** under similar conditions, the yield of products was capricious in nature and difficult to reproduce. The excessive amounts of $AlCl_3$ required for these procedures and the irregularities of reaction results were undesirable, hampering the preparation of sufficient quantities of material for analog studies. Thus, improved conditions were required.

Intuitively, the apparent lack of reactivity of, for example **4**, under these conditions may be due to the reduced nucleophilicity at C3 as a result of the halogen substitutions on the azaindole ring. Results of AM1 optimization calculations showed that both the delocalization of negative electrostatic potential and the HOMO orbital distribution were substantially decreased in **4** when compared to the parent azaindole **6** (Fig. 3).[3,4] In studies of Friedel–Crafts acylation of indoles using the strongly acidic ionic liquid 1-ethyl-3-methylimidazolium chloroaluminate (generated from

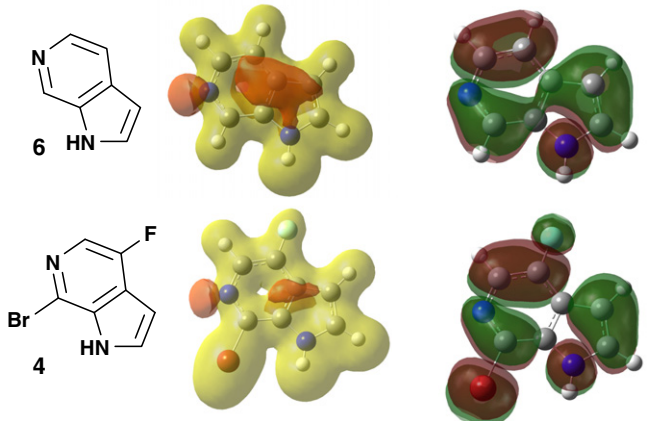
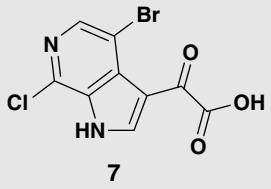
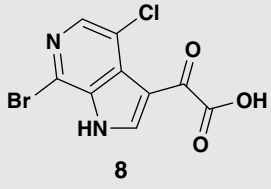
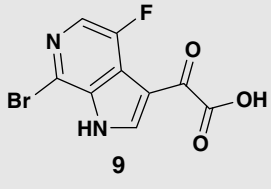
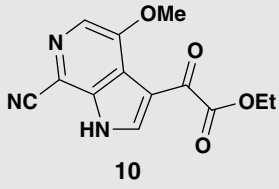
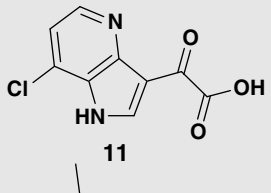
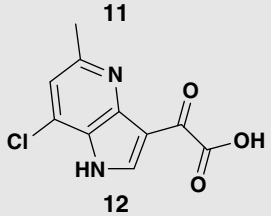
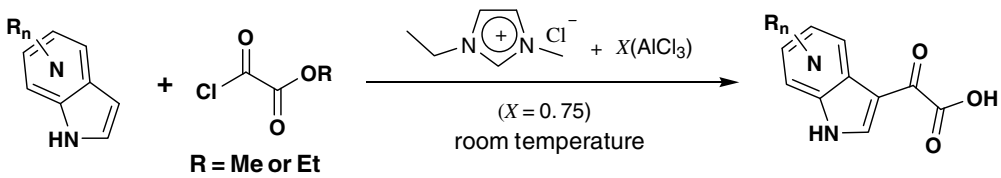


Figure 3. Center column: negative electrostatic potential; right column: HOMO orbital.[3]

Table 1

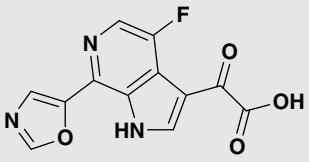
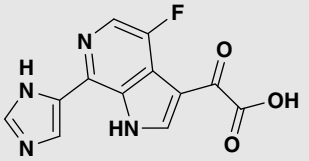
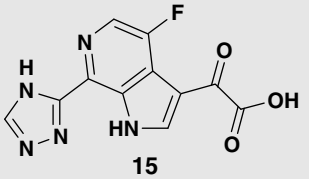
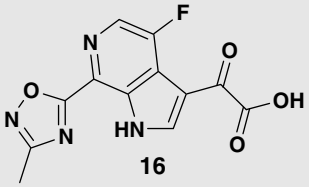
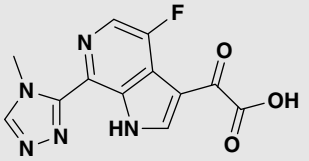
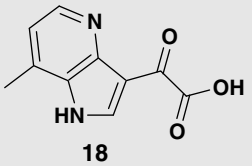
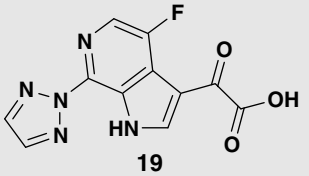
Entry	Product	Yield (%)
1	 **7**	93
2	 **8**	88
3	 **9**	80
4	 **10**	63[a]
5	 **11**	84[b]
6	 **12**	43[b]

[a] The reaction mixture was quenched after 3 h to minimize 4-demethylation.
[b] 3–4 equiv of methyl chlorooxoacetate was used for these two examples.



Scheme 1.

Table 2

Entry	Product	Purity[a] (%)
1	 **13**	90
2	 **14**	90
3	 **15**	87
4	 **16**	90
5	 **17**	84
6	 **18**	80[b]
7	 **19**	77

[a] % Purities were determined by reverse phase HPLC.[11]

[b] 3 equiv of methyl chlorooxoacetate and 4 equiv of $AlCl_3$ ($X = 0.67$) were used.

1-ethyl-3-methylimidazolium chloride (EmimCl) and aluminum chloride ($X(AlCl_3)$, mole fraction $X = 0.67–0.75$), it was observed that these conditions appeared to be more generally applicable for less electron rich indole ring systems.[5] Thus, it was considered that the imidazolium ionic liquid might activate electron-deficient substituted azaindoles, possibly by influencing electron distribution.[6]

When these conditions (2 equiv of 1-ethyl-3-methylimidazolium chloride (EmimCl), 4 equiv of $AlCl_3$ ($X = 0.67$); 2 equiv of ethyl chlorooxoacetate; rt) were applied to the 6-azaindole **1**, no reaction was observed. However, when the amount of $AlCl_3$ was increased to 6 equiv ($X = 0.75$), a rapid acylation reaction occurred within a few hours. The formation of the ester was observed by LC/MS but this was hydrolyzed to the acid under the extended reaction time (Scheme 1). This gave the 3-glyoxylic acid **7** (Table 1) in high yield after 18 h at ambient temperature. For subsequent amide formation, it was thus convenient to obtain the acid directly in one pot. These conditions[7] were used for the acylation of a series of 4- and 6-azaindoles, including **4** and **5**, to obtain the corresponding 3-glyoxylic acids in useful yields, as summarized in Table 1.[8] For the acylation of 7-cyano-4-methoxy-6-azaindole (**3**), 4-demethylation was observed under these conditions. However, this side reaction could be minimized by quenching the reaction after 3 h to obtain the ethyl ester **10** in 63% yield.[9] A number of analogs of 6-azaindole **4** incorporating heterocycles at C7, including oxazole, imidazole, triazole, and oxadiazole,[10] also underwent efficient reaction under the strongly acidic EmimCl–$AlCl_3$ acylation conditions (Table 2). The products obtained were of sufficient purity that they could be used directly in the subsequent amide bond forming reaction.

In summary, this work has demonstrated that electron-deficient, substituted azaindoles that are recalcitrant to standard acylation conditions could be efficiently acylated by using a modified imidazolium chloroaluminate ionic liquid-promoted Friedel–Crafts acylation. Various heterocycles were well tolerated under the strongly acidic conditions. This one-pot acylation/hydrolysis reaction procedure provides a convenient way to obtain substituted azaindole-3-glyoxylic acids suitable for the rapid generation of analogs for the development of SAR associated with HIV attachment inhibitors.

Acknowledgments

We thank Dr. Nicholas A. Meanwell for support of this work, and Dr. Yi Li for performing the initial calculations on atomic charges of 6-azaindoles **4** and **6**.

References and notes

1. Kadow, J. F.; Wang, H.-G. H.; Lin, P.-F. *Curr. Opin. Invest. Drugs* **2006**, *7*, 721.
2. Zhang, Z.; Yang, Z.; Wong, H.; Zhu, J.; Meanwell, N. A.; Kadow, J. F.; Wang, T. *J. Org. Chem.* **2002**, *67*, 6226 and references cited therein. It was reported that methyl 3-glyoxylates of 4- and 6-azaindoles were obtained in 42% yield from the corresponding parent azaindoles using 5 equiv of $AlCl_3$ and 5 equiv of methyl chlorooxoacetate in CH_2Cl_2 at rt. It was also noted that 5- and 7-azaindoles provided C3 acylated products in higher yields than 4- and 6-azaindoles.
3. Energy optimizations were performed using AMPAC 8.15 GUI with AM1 parameters. Calculations were run with tight convergence criteria and calculated electrostatic potential (ESP) charges turned on. Both HOMO and ESP displays were extracted directly from AMPAC displays of the resulting vis files. ESP maps were contoured at −0.055 (hartrees), while HOMO maps were contoured at 0.005 (cubic bohrs).
4. Calculations of atomic charges from electrostatic potential of LMP2/LACVP** geometries[a,b] revealed that the N1–C2–C3 portion of **4** was different from that of the parent unsubstituted azaindole **6**. The C3 atom of **4** bore charges of −0.19, while the charge at C3 atom of **6** was −0.59. (a) Sæbø, S.; Pulay, P. *Ann. Rev. Phys. Chem.* **1993**, *44*, 213; (b) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257.
5. Yeung, K.-S.; Farkas, M. E.; Qiu, Z.; Yang, Z. *Tetrahedron Lett.* **2002**, *43*, 5793.
6. An ab initio study of the benzene–$AlCl_3$ complex indicated a strong electrostatic interaction between benzene and $AlCl_3$, and that the benzene carbon atom closest to the Al atom was rendered highly nucleophilic. Tarakeshwar, P.; Lee, J. Y.; Kim, K. S. *J. Phy. Chem. A* **1998**, *102*, 2253; It is conceivable that the chloroaluminate species, $Al_2Cl_7^-/Al_3Cl_{10}^-$, present in the ionic liquid EmimCl–$X(AlCl_3)$ ($X = 0.75$) may exert a similar but more pronounced effect on the 4- and 6-azaindoles. It was also proposed that in the ionic liquid, the acylating agent is the free acylium ion. Adam, C. J.; Earle, M. J.; Roberts, G.; Seddon, K. R. *Chem. Commun.* **1998**, 2097. and references cited therein.
7. $AlCl_3$ (anhydrous powder packaged under argon in ampoules purchased from Aldrich) and EmimCl (purchased from TCI) were used as received. A typical experimental procedure is as follows: azaindole (1 equiv) was added to the imidazolium chloroaluminate ($X = 0.75$) ionic liquid (prepared as described in Ref. 5) under a nitrogen atmosphere, and the reaction mixture stirred until a

homogenous mixture resulted. Ethyl or methyl chlorooxoacetate (2 equiv) was added and the reaction mixture stirred at ambient temperature until complete formation of the acid. The mixture was cooled in an ice-water bath and quenched by carefully adding excess ice water. The precipitates formed were filtered and were further washed with excess water. Purification of the product was performed by chromatography or recrystallization.

8. Compound **7**: ^{1}H NMR (500 MHz, CD_3OD) δ 8.61 (s, 1H), 8.24 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 180.4, 165.0, 142.5, 141.3, 134.3, 131.5, 131.3, 113.7, 110.7; compound **9**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.41 (br s, 1H), 8.58 (s, 1H), 8.57 (s, 1H); compound **10**: ^{1}H NMR (500 MHz, CD_3OD) δ 8.42 (s, 1H), 8.17 (s, 1H), 4.40 (q, J = 7.0 Hz, 2H), 4.10 (s, 3H), 1.36 (t, J = 7.0 Hz, 3H); compound **11**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.65 (br s, 1H), 8.75 (s, 1H), 8.53 (d, J = 5.5 Hz, 1H), 7.65 (d, J = 5.5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 180.6, 164.7, 143.5, 142.0, 140.4, 129.4, 128.2, 118.7, 111.6.
9. As illustrated by this example, the ester could be obtained by monitoring the reaction progress and quenching the reaction mixture before the hydrolysis to the acid occurred to a certain extent. Interestingly, the 4-bromo analog of 6-azaindole **3** could not be acylated under these conditions.
10. Although the C7 imidazole and the 1,2,4-triazole moieties of the starting materials for entries 2 and 3, respectively, of Table 2 may also be acylated, the acylated azole moieties were most likely unstable and underwent hydrolysis under these conditions or during the aqueous work-up.
11. Samples were analyzed by a Shimadzu VP/Waters Micromass LC/MS system, and the following reverse phase HPLC conditions were used: solvent A = 10% MeOH–90% H_2O–0.1% TFA; solvent B = 90% MeOH–10% H_2O–0.1% TFA; start %B = 0, final %B = 100; flow rate = 5 ml/min; gradient time = 2 min; stop time = 3 min; UV detection wavelength 220 nm; YMC ODS-A C18 S7 3.0 $\times$ 50 mm column.