

A General and Efficient Five-Step One-Pot Procedure Leading to Nitrogen-Bridgehead Heterocycles Containing an Imidazole Ring

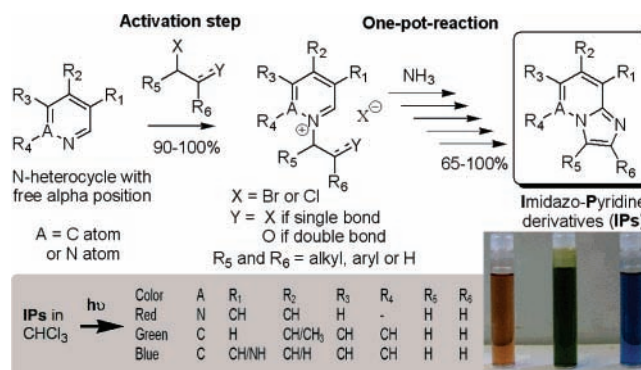
Alexis D. C. Parenty, Yu-Fei Song, Craig J. Richmond, and Leroy Cronin*

Chemistry Department, WestCHEM, University of Glasgow,
Glasgow, G12 8QQ, United Kingdom

l.cronin@chem.gla.ac.uk

Received February 2, 2007

ABSTRACT



A very simple annulation reaction was designed, allowing an imidazole moiety to be fused onto a range of pyridine-based derivatives. The methodology consists of an activation step via the formation of a pyridinium salt to increase the electrophilicity of the pyridine ring, followed by a cascade reaction triggered by a nucleophilic attack of the iminium moiety. Depending on the pyridinium salt, it is possible to obtain functionalized imidazole moieties.

A great deal of research in heterocyclic chemistry is concerned with discovering new methods of ring formation. Most classical methodologies for synthesis of heterocyclic compounds continue to be used widely; nevertheless, due to improvement in screening methods in the pharmaceutical industry, there is a constant need for novel methods that can be carried out under simpler, milder, or more effective conditions.¹ In this respect, methodologies leading to the synthesis of nitrogen-bridgehead heterocycles containing an imidazole ring are particularly appealing because this moiety is a common structural motif in biologically active compounds produced by nature.² Imidazo[1,2-*a*]pyridine deriva-

tives (**IPs**) are probably the most widely used heterocyclic system from the bridged-imidazole group and form the framework of marketed drugs like Zolpidem, Olprinone, and Divalpon, as well as other pharmacologically important molecules.³ The imidazole moiety can also be involved in the formation of a stable radical leading to interesting photochemical properties.⁴ Furthermore, due to the possible formation of stable N-heterocyclic carbenes (NHCs), the

(1) Gilchrist, T. L. In *Heterocyclic Chemistry*, 3rd ed.; Addison Wesley: Essex, England, 1997; p 414.

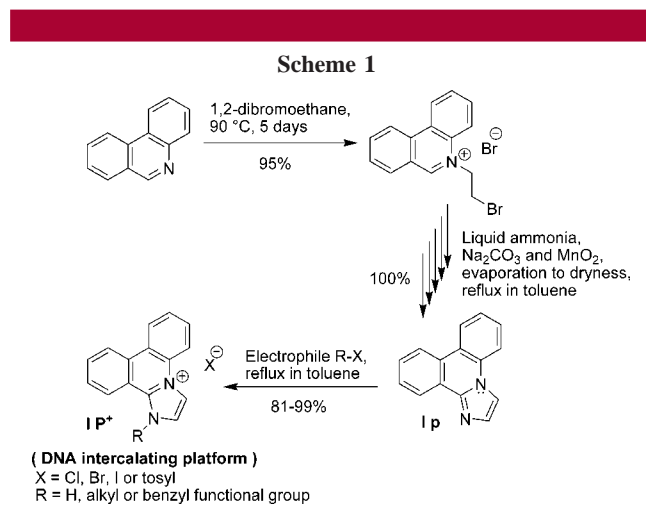
(2) Jin, Z. *Nat. Prod. Rep.* **2005**, 22, 196.

(3) (a) Enguehard-Gueiffier, C.; Hubner, H.; El Hakmaoui, A.; Allouchi, H.; Gmeiner, P.; Argiolas, A.; Melis, M. R.; Gueiffier, A. *J. Med. Chem.* **2006**, 49, 3938. (b) Mattner, F.; Mardon, K.; Loc'h, C.; Katsifis, A. *Life Sci.* **2006**, 79, 287. (c) Schmid, S.; Schuhle, D.; Austel, V. *Synthesis* **2006**, 12, 2031.

(4) (a) Arduengo, A. J.; Tapu, D.; Marshall, W. J. *Angew. Chem., Int. Ed.* **2005**, 44, 7240. (b) Garrison, J. C.; Youngs, W. J. *Chem. Rev.* **2005**, 105, 3978. (c) Spencer, L. P.; Beddie, C.; Hall, M. B.; Fryzuk, M. D. *J. Am. Chem. Soc.* **2006**, 128, 12531.

imidazole moiety has found wide-ranging applications in coordination chemistry,⁵ organometallic catalysis such as cross-coupling reactions,⁶ asymmetric catalysis,⁷ and oxidation.⁸ With these in mind, there have been great efforts to discover and optimize new reactions that will facilitate the construction of imidazo[1,2-*a*]pyridine derivatives (**Ips**).

Recently, we have reported a five-step one-pot methodology leading to the fusion of an unsubstituted imidazole moiety onto a phenanthridine framework to form imidazo[1,2-*f*]phenanthridine (**Ip**, Scheme 1), subsequently used for



the synthesis of a new cationic DNA intercalating platform, imidazo[1,2-*f*]phenanthridinium (**IP⁺**).⁹

The reported methodology has several advantages over classical synthetic routes that lead to similar imidazo-fused heterocycles:¹⁰ First, the procedure is overall more effective and simpler as the possible side products and excess reactants are either in the gaseous state at room temperature or insoluble in the solvent system used. Second, the starting material phenanthridine does not require its α position to be functionalized at some point by an amino group, frequently obtained via the Chichibabin reaction, or by a regioselective

halogenation followed by nucleophilic substitution by ammonia.

During this previous investigation, it was observed that a chloroform solution of the phenanthridine intermediate **Ip** (Scheme 1) showed an unusual degree of photochromic behavior, turning rapidly to blue under daylight.⁹ This unusual behavior, as well as the significant demand for imidazo-fused heterocycles, prompted us to develop similar annulation reactions onto N-heteroaromatic systems other than phenanthridine. Herein, we report the modification and generalization of our previously reported methodology to allow the synthesis of a range of imidazo-pyridine-like derivatives **Ips 6a–i** from various pyridine-like heterocycles (Table 1 and Scheme 2, left-hand side). We also describe a

Table 1.

#	structure and color ^a	yield % ^{b,c}	#	structure and color	yield % ^{a,b}
6a		100 ^a	6f		98 ^a
6b		65 ^a	6g		85 ^b
6c		100 ^a	6h		88 ^b
6d		100 ^a	6i		100 ^b
6e		92 ^a			

^a Coloration of the chloroform solution of **Ips** when left exposed to daylight for 1–2 days. ^b With Method 1. ^c With Method 2.

similar approach with ketone derivatives **7g–i** leading to the possible derivatization of the imidazole moiety of **Ip 6g–i** (Table 1 and Scheme 2, right-hand side).

Once more, it was observed that the **Ip** frameworks with an unsubstituted imidazole moiety **6a–f** display light sensitivity in a chloroform solution. Depending on the substituent around the pyridine central core, **Ip** can turn from colorless to red (**6e**), blue (**6a** and **6f**), cyan (**6c**), or green (**6b** and **6d**) in a matter of hours when left exposed to daylight (see the color code in Table 1). Surprisingly, **Ip** frameworks with an imidazole moiety bearing a substituent on R₅ or R₆ (**6g–i**) stay colorless even when exposed to the stronger irradiation of a UV lamp.

Both methodologies consist of an activation step (top part of Scheme 2) and a 5-step cascade reaction (bottom part of

(5) (a) Campeau, L. C.; Thansandote, P.; Fagnou, K. *Org. Lett.* **2005**, 7, 1857. (b) Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Org. Lett.* **2005**, 7, 1991. (c) Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Org. Lett.* **2005**, 7, 3805.

(6) (a) Alexandre, F.; Baltaze, J. P.; Roland, S.; Mangeney, P. J. *Organomet. Chem.* **2006**, 691, 3498. (b) Cesar, V.; Bellemin-Lapomnaz, S.; Gade, L. H. *Chem. Soc. Rev.* **2004**, 33, 619. (c) Li, S. J.; Zhong, J. H.; Wang, Y. G. *Tetrahedron: Asymmetry* **2006**, 17, 1650. (d) Martin, D.; Kehrli, S.; d'Augustin, M.; Clavier, H.; Mauduit, M.; Alexakis, A. *J. Am. Chem. Soc.* **2006**, 128, 8416.

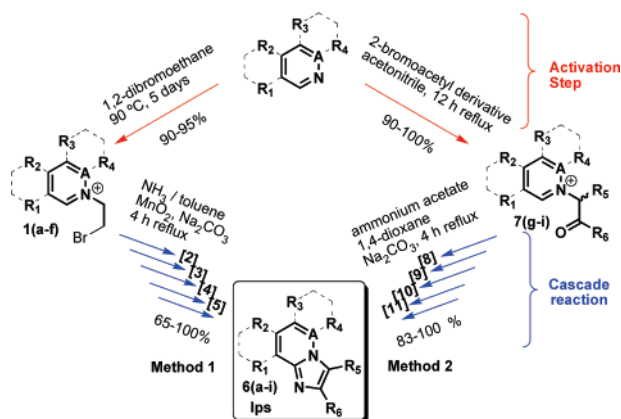
(7) Nielsen, R. J.; Goddard, W. A. *J. Am. Chem. Soc.* **2006**, 128, 9651.

(8) (a) Clyne, M. A.; Aldabbagh, F. *Org. Biomol. Chem.* **2006**, 4, 268. (b) Kiepek, E.; Zhou, Y. H.; Hoz, S.; Rozenal, E.; Kazmaier, P. M.; Buncel, E. *Can. J. Chem.* **2005**, 83, 1448. (c) Luneau, D.; Rey, P. *Coord. Chem. Rev.* **2005**, 249, 2591. (d) Plutecka, A.; Hoffmann, M.; Rychlewska, U.; Kucybała, Z.; Paczkowski, J.; Pyszka, I. *Acta Crystallogr., Sect. B: Struct. Sci.* **2006**, 62, 135.

(9) Parenty, A. D. C.; Guthrie, K. M.; Song, Y. F.; Smith, L. V.; Burkholder, E.; Cronin, L. *Chem. Commun.* **2006**, 11, 1194.

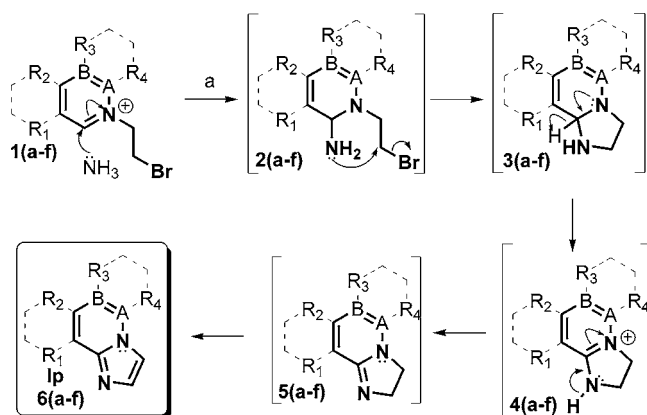
(10) (a) Cooper, G.; Irwin, W. J. *J. Chem. Soc., Perkin Trans. 1* **1976**, 19, 2038. (b) Hand, E. S.; Paudler, W. W. *J. Org. Chem.* **1978**, 43, 2900. (c) Hubert, A. J.; Reimling, H. *Chem. Ber. Recl.* **1970**, 103, 3811. (d) Ito, S.; Kakehi, A.; Miwa, T. *Heterocycles* **1991**, 32, 2373. (e) Tomoda, H.; Hirano, T.; Saito, S.; Mutai, T.; Araki, K. *Bull. Chem. Soc. Jpn.* **1999**, 72, 1327.

Scheme 2



Scheme 2). In the activation step, the pyridine-like heterocycle undergoes a nucleophilic substitution on 1,2-dibromoethane or on a 2-bromoacetyl derivative (left-hand side and right-hand side of Scheme 2) to yield the highly electrophilic cationic reactant **1a–f** or **7g–i**, respectively. Subsequent cascade reactions in Methods 1 and 2 are discussed below.

We have previously reported substantial evidence in the specific example of phenanthridine derivative **6a**⁹ to be able to propose a general mechanism for the cascade reaction of Method 1 (Schemes 2 and 3).

Scheme 3^a

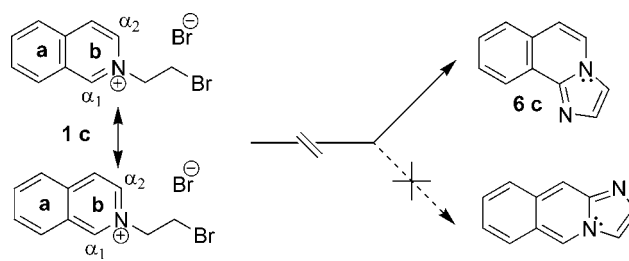
^a Reaction conditions: (a) NH_3 /toluene, MnO_2 , Na_2CO_3 , 4 h reflux.

The reaction is initiated by nucleophilic attack of the highly reactive iminium moiety of the pyridinium derivative **1** by ammonia (Scheme 3). The resulting adduct **2** undergoes an intramolecular 5-membered-ring cyclization to form intermediate **3**, which then undergoes a loss of hydride followed by a deprotonation step yielding the dihydroimidazo intermediate **5**. The final oxidation step occurs at higher temperature, when the toluene is brought to reflux. The corresponding unsubstituted imidazopyridine (**Ip**) derivatives **6a–f** are simply recovered after filtering off the inorganic side products from the solution.

To generalize the methodology to diverse N-heterocyclic starting materials **1a–f**, it was necessary to modify the previously reported method,⁹ which nevertheless provided quantitative yield with the specific example of **Ip** phenanthridine derivative **6a** (Scheme 1, Table 1). Attempting to synthesize the quinoline derivative **6b** (Table 1) with the earlier methodology⁹ led to unidentified side product contamination. This could be due to a redox side-reaction between the hydride donor intermediate **3b** and starting material **1b** (Scheme 3), both residing in the ammonia solution. This redox reaction was previously studied and well understood.¹¹ Therefore, to prevent such a side reaction, it was necessary to find a way to separate **3a–f** from **1a–f** (Scheme 3), and this was accomplished by means of a phase transfer reaction between toluene and ammonia. Under these biphasic conditions, cationic starting material **1a–f** remains in the more polar ammonia phase, whereas the neutral intermediates **2a–f** and **3a–f** shift toward the apolar toluene phase as soon as they form, avoiding any side-reaction with reactant **1a–f**. Accordingly, it was possible to isolate analytically pure **Ip**, **6a–f**, in high yield by simple filtration and concentration of the mother liquor, without need of any further purification. The reason for the relatively lower yield of **6b** (Table 1) is not fully understood, but this could come from either a higher adsorption of the molecule on the inorganic residue (MnO_2 , Na_2CO_3 , and NaBr), impairing its extraction during the filtration step, or unidentified side product(s), insoluble in the extraction solvent.

It is interesting to note that the cascade reaction of Method 1 occurs in a regioselective manner in the case of **6c** (Table 1 and Scheme 4). Starting material **1c** has two available α

Scheme 4



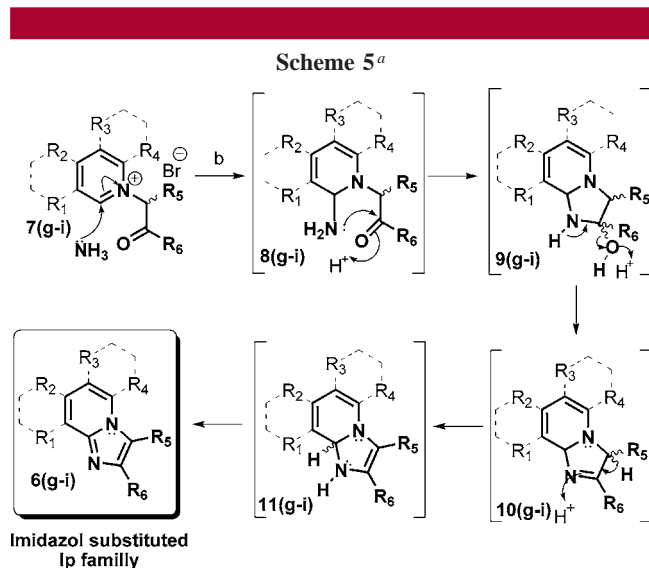
positions (α_1 and α_2 ; Scheme 4); nevertheless, the first nucleophilic addition step only takes place on α_1 . In this way, only the aromaticity of the heterocycle **b** (Scheme 4) is lost during the nucleophilic attack leading to the first intermediate **2c** (Scheme 3). Indeed, nucleophilic addition of ammonia onto the other α position is not thermodynamically favored because it would lead to the loss of aromaticity in both cycles **a** and **b** (Scheme 4). The structure of **6c** was unambiguously confirmed by the absence of singlets in the ^1H NMR signal.

To increase even further the flexibility of the methodology, we became interested in obtaining **Ips** with additional

(11) Parenty, A. D. C.; Smith, L. V.; Pickering, A. L.; Long, D. L.; Cronin, L. *J. Org. Chem.* **2004**, *69*, 5934.

substituents on the imidazole moiety (R_5 and R_6 , Scheme 2, right-hand side). A similar approach to Method 1 was originally attempted. However, the activation step necessary for the synthesis of the corresponding 2-bromoethyl-substituted starting material **1** was problematic. First, there are not many 1,2-dibromoethane derivatives commercially available; second, there is no regioselectivity during the substitution reaction as both halogen atoms of the 1,2-dibromoethane derivatives can react equally; finally, there is formation of additional side products coming from a competitive elimination reaction.

Therefore, another strategy was designed using the more readily available 2-haloacetyl derivatives (Scheme 2, right-hand side; and Scheme 5). In this approach, liquid ammonia



^a Reaction conditions: (a) 1,4-dioxane, ammonium acetate, MnO_2 , reflux for 4 h, then addition of Na_2CO_3 followed by diethyl ether and filtration.

could not be used as a nucleophile since the carbonyl moiety of **7g-i** enhances the acidity of the adjacent methylene position next to the ammonium moiety and leads, in such basic conditions, to a stabilized ylide that undertakes

cycloaddition side reactions.¹² Instead, ammonium acetate was used as a mild source of ammonia.

The condensation reaction between the amino group and ketone (**8g-i** to **10g-i**) was used to both close the 5-membered ring and form the first $C=N$ double bond. In the acidic conditions of the reaction, the imine functional group of **10g-i** isomerizes to an enamine **11g-i**, due to the stabilizing interactions of the lone pairs of the two adjacent nitrogen atoms. Finally, the resulting dihydroimidazole **11g-i** is spontaneously oxidized by MnO_2 to imidazole derivative **6g-i**, favored by a strong re-aromatization driving force.

Note that it was not possible to obtain unsubstituted imidazole derivatives **6a-f** by using this second methodology since the required acetaldehyde starting material **7** ($R_5 = R_6 = H$) (Scheme 5) could not be obtained during the activation step (Scheme 2). This is because attempted reactions of chloroacetaldehyde with pyridine derivatives invariably lead to a polymerization side reaction via aldol condensation.

In conclusion, we have developed two simple, general, and complementary one-pot methodologies leading to imidazo[1,2-*a*]pyridine derivatives **Ips**. The first one leads to an unsubstituted imidazole moiety whereas the second one allows further derivatizations on the imidazole ring of **Ips** at R_5 and R_6 positions (Scheme 2). It was observed that Method 1, leading to unsubstituted imidazole **Ips**, invariably produces derivatives that are light sensitive. In chloroform solution, deep coloration ranging from blue, red, cyan, and green could be obtained by exposure to daylight in a matter of hours. The mechanism of the photochromic reaction that takes place upon UV irradiation of unsubstituted **Ip** derivatives **6a-f** remains to be elucidated. Further investigations are underway and this work will be reported in the near future.

Supporting Information Available: Detailed reaction protocols as well as compound analytical data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL070263Z

(12) (a) Fang, X.; Wu, Y. M.; Deng, J.; Wang, S. W. *Tetrahedron* **2004**, *60*, 5487. (b) Krauze, A.; Vitolina, R.; Garaliene, V.; Sile, L.; Klusa, V.; Duburs, G. *Eur. J. Med. Chem.* **2005**, *40*, 1163.