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

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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. 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. Imidazo[1,2-a]pyridine derivatives (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. The imidazole moiety can also be involved in the formation of a stable radical leading to interesting photochemical properties. Furthermore, due to the possible formation of stable N-heterocyclic carbenes (NHCs), the

imidazole moiety has found wide-ranging applications in coordination chemistry, organometallic catalysis such as cross-coupling reactions, asymmetric catalysis, and oxidation. 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+). The reported methodology has several advantages over classical synthetic routes that lead to similar imidazo-fused heterocycles: 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 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. 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 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 Scheme 2).
Scheme 2). In the activation step, the pyridine-like hetero-cycle undergoes a nucleophilic substitution on 1,2-dibromo-ethane 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 6a9 to be able to propose a general mechanism for the cascade reaction of Method 1 (Schemes 2 and 3).

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 (MnO2, Na2CO3, 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 positions (α1 and α2; Scheme 4); nevertheless, the first nucleophilic addition step only takes place on α1. 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

substituants on the imidazole moiety (R₅ and R₆, 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 I 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 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. 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 MnO₂ 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 (R₅ = R₆ = 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 1ps. The first one leads to an unsubstituted imidazole moiety whereas the second one allows further derivatizations on the imidazole ring of 1ps at R₅ and R₆ positions (Scheme 2). It was observed that Method 1, leading to unsubstituted imidazole 1ps, 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 1p 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.

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