Formation of Nitrogen-containing Heterocycles Using Di(imidazole-1-yl)methanimine

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A mild and efficient synthesis of five- and six-membered nitrogen containing heterocyclic compounds, in which di(imidazole-1-yl)methanimine serves as a one-carbon source, is reported.

Many natural products and synthetic pharmaceuticals contain heterocyclic groups, which often play an essential role in their biological activity [1]. Cyanogen halides have been widely used in the preparation of nitrogen-containing heterocycles *via* a double attack by the nitrogen and another heteroatom nucleophile (e.g. O, S, N); however they suffer many drawbacks, including high volatility and high toxicity [2]. In addition, cyanogen bromide reacts readily with tertiary amines and thioethers, *via* the Von Braun reaction, yielding cyanamides and thiocyanates respectively [3]. Therefore, such a transformation is not suitable in molecules containing these functional groups. Thus, there is a need for alternative reagents.

Di(imidazole-1-yl)methanimine (**1**) has been previously reported as a coupling reagent for the formation of phosphodiester bonds [4], and our laboratory has recently reported its new usage as a direct guanylating reagent [5]. To this end, we herein wish to report a mild and efficient synthesis of five- and six-membered N-heterocycles, in which **1** serves as a one-carbon source.
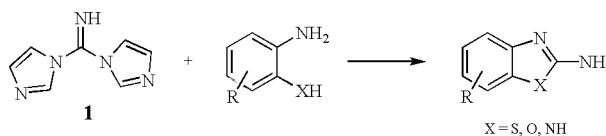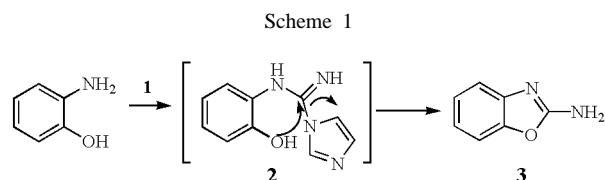

Table 1

Entry	Nucleophile	Conditions	Products	Yield[a,b]
1		THF/reflux 6 h		94%
2		THF/rt 12 h		71%[c]
3		THF/reflux 12 h		59%[c]
4		THF/reflux 12 h		88%
5		THF/reflux 12 h		50%
6		DMF/90°C 12 h		28%
7		THF/reflux 24 h		34%
8		THF/reflux 12 h		61%[c]
9		THF/reflux 12 h		83%[c]
10		THF/reflux 12 h		47%

[a] Isolated yield; [b] The reaction conditions are not optimized; [c] Products compared with commercially available authentic samples.

Titled compound **1** was synthesized by treating cyanogen bromide with imidazole based on a previously reported procedure [4,5].

Using benzoxazole **3** (entry 1) as an example shown in Scheme 1, mechanistically, the reaction between **1** and 2-aminophenol involves the displacement of the first imidazole group of **1** by the amine, affording imidazole carboximidamide, intermediate **2**. In turn, **2** undergoes cyclization through nucleophilic attack of the phenol oxygen atom, forming the N-heterocyclic compound (entry 1). The reaction results, along with additional substrates, illustrating the scope of this reaction, are summarized in Table 1.

Scheme 1

As shown in Table 1, the reaction went smoothly with 2-substituted anilines (O, S, N), regardless of their nucleophilicity (entry 1-3). This may suggest that the second imidazole displacement is not the rate-limiting step due to the strong tendency towards cyclization. Compounds bearing either an electron-withdrawing group (entry 4) or electron-donating group (entry 5) were also tested, and found to form the desired products with good to excellent yield. In addition, no dealkylation product at the tertiary amine site was observed (entry 5). A sterically hindered and deactivated substrate (entry 6) could also generate the desired product, albeit with low yield, when the reaction temperature was raised. Collectively, these examples suggest that the cyclization reaction using **1** may occur with a wide diversity of starting anilines under mild conditions. Given the example that 2-aminobenzimidazole is an attractive template for urokinase inhibitors [6], the reaction with **1** could be useful in the formation of many bioactive heterocyclic compounds.

Although 2-aminobenzyl alcohol did form the six-membered cyclic compound (entry 7), the reaction was relatively sluggish and low yielding. The reason may be the lack of a driving force to form an aromatic system. On the other hand, the reaction between anthranilic acid and **1** in refluxing THF led to the formation of quinazolinedione (entry 8), and apparently occurred *via* intermediate **4**, which has been known to undergo rearrangement under either acidic or basic conditions (Scheme 2) [7]. The displaced imidazole in this case might serve as a base to promote the reaction.

Additional examples included the synthesis of the 2-amino-1,3,4-oxadiazole analog (entry 9) [8], which was converted cleanly in excellent yield from benzoic

Scheme 2
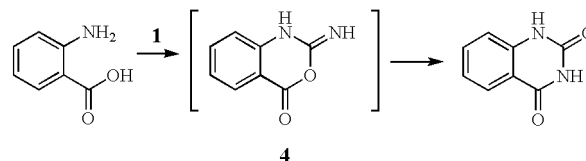
hydrazide, and the synthesis of a fused ring compound with a nitrogen atom at the ring junction (entry 10) [9], from 2-pyridinehydrazine.

It is worthy to note that **1** is a solid and therefore is much easier to handle in the experiments than cyanogen halides. The imidazole generated as a side product could be removed by successive washing with water and saturated NH_4Cl, simplifying the purification process. Furthermore, environmentally safe imidazole could be recycled into the preparation of compound **1**. However, unlike its analogous carbonyldiimidazole, which was extensively used in organic synthesis, compound **1**, in our opinion, has been underused. Hopefully, the above demonstrations, along with our recent study of its usage in the synthesis of guanidines [5], would inspire new exploration of its potential usage in synthesis.

In summary, we have found and successfully demonstrated the variability of di(imidazole-1-yl)methanimine as a useful reagent for the formation of N-heterocyclic compounds.

EXPERIMENTAL

General Methods.

All commercially available starting materials and solvents were reagent grade. Anhydrous tetrahydrofuran (THF) and dimethylformamide (DMF) were used. Analytical thin-layer chromatography was carried out using Merck DC-F_{254} precoated silica gel plates. Flash chromatography was performed using kieselgel 60 (230-400 mesh) silica gel. ^1H and ^{13}C NMR spectra were recorded on a 400 MHz instrument. Chemical shifts are reported in parts per million (ppm). Mass spectral analyses were performed on a GC- or LC-MS. Elemental analyses were determined and are within $\pm$ 0.4% of the calculated values unless otherwise noted.

Di(imidazole-1-yl)methanimine (**1**).

To a solution of imidazole (6.8 g, 100 mmol) in 500 mL dichloromethane was added cyanogen bromide (3.7 g, 33 mmol) and the mixture heated at reflux temperature for 30 min. The mixture was cooled to rt., the white precipitate removed by filtration and the filtrate concentrated to 50 mL and cooled to 0 °C for 2 days. The crystallized solid was filtered and washed with cold dichloromethane and dried to give 4.4 g (81%) of **1** as a white solid: ^1H NMR, (DMSO-d_6): δ 7.13 (s, 1H); 7.58 (s, 1H); 8.10 (s, 1H); 10.24 (s, 1H); ^{13}C NMR, (DMSO-d_6) δ 119.3; 130.1; 137.8; 141.3.

Typical Experimental Procedure for Entry **1-10**.

Benzooxazol-2-ylamine (**entry 1**).

A solution containing di(imidazole-1-yl)methanimine **1** (161 mg, 1.0 mmol) and 2-aminophenol (109 mg, 1.0 mmol) in anhydrous THF (5 mL) was allowed to reflux under nitrogen overnight. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (20 mL), and washed successively with water, saturated aqueous NH_4Cl solution and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the crude product. Further purification by silica gel gave the desired product as a white solid (126 mg, 94% yield). The MS gave the molecular ion (M+) 134. $R_f = 0.7$ (EtOAc). MP 130-132 °C; ^{1}H NMR ($CDCl_3$): δ 7.33 (d, 1H, $J =$ 8.0 Hz), 7.25 (d, 1H, $J = 8.0$ Hz), 7.16 (t, 1H, $J = 8.0$ Hz), 7.07 (t, 1H, $J = 8.0$ Hz), 6.17 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 162.7, 148.9, 143.0, 128.8, 124.4, 116.6, 109.4.

Benzothiazol-2-ylamine (**entry 2**).

The compound was obtained as a white solid. The MS gave the molecular ion (M+)150. mp 125-127 °C; ^{1}H NMR (DMSO-d$_6$): δ 7.63 (d, 1H, $J = 8.0$ Hz), 7.47 (br, 2H), 7.36 (d, 1H, $J = 8.0$ Hz), 7.21 (t, 1H, $J = 8.0$ Hz), 7.00 (t, 1H, $J = 8.0$ Hz).

1*H*-Benzoimidazole-2-ylamine (**entry 3**).

The compound was obtained as a white solid. The MS gave the molecular ion (M+) 133. mp 226-228 °C; ^{1}H NMR ($CDCl_3$): δ 7.28 (d, 2H, $J = 8.0$ Hz), 6.86 (d, 2H, $J = 8.0$ Hz), 6.25 (s, 1H), 4.71 (br, 2H).

5-Nitro-benzooxazol-2-ylamine (**entry 4**).

The compound was obtained as a white solid. The MS gave the molecular ion (M+) 179. mp 300°C; ^{1}H NMR ($CDCl_3$): δ 8.06 (m, 2H), 7.46 (d, 1H, $J = 8.0$ Hz), 6.20 (br, 2H).

6-Piperidin-1-yl-benzooxazol-2-ylamine (**entry 5**).

The compound was obtained as a white solid. The MS gave the molecular ion (M+) 217. mp 175-181 °C; ^{1}H NMR ($CDCl_3$): δ 7.24 (d, 1H, $J = 8.0$ Hz), 6.89 (s, 1H), 6.83(d, 1H, $J = 8.0$ Hz) 5.92 (br, 2H), 3.30 (m, 4H), 1.77-2.05 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 159.7, 151.1, 142.2, 130.8, 125.4, 112.12, 98.8, 50.3, 26.8, 25.1.

Anal.Calcd. for $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96; N, 19.34. Found C, 66.06; H, 7.03; N, 19.40.

1-Phenyl-1*H*-benzoimidazole-2-ylamine (**entry 6**).

The compound was obtained as a white solid. The MS gave the molecular ion (M+) 209. mp 150-154 °C; ^{1}H NMR (DMSO-d$_6$): δ 6.67-7.35 (m, 9H, aromatic), 5.79 (br, 2H).

4*H*-Benzo[*d*][1,3]oxazin-2-ylamine (**entry 7**).

The compound was obtained as a white solid. The MS gave the molecular ion (M+) 148. mp 163-166 °C; ^{1}H NMR (DMSO-d$_6$): δ 7.25 (d, 1H, $J = 8.0$ Hz), 7.02 (d, 1H), 6.89 (d, 1H, $J = 8.0$ Hz), 6.80 (d, 1H, $J = 8.0$ Hz), 6.68 (br, 2H), 5.15 (s, 2H).

1*H*-Quinazoline-2,4-dione (**entry 8**).

The compound was obtained as a white solid. The MS gave the molecular ion (M+) 162. mp 295-300 °C; ^{1}H NMR (DMSO-d$_6$): δ 11.21 (br, 2H), 7.89 (d, 1H, $J = 8.0$ Hz), 7.61 (t, 1H, $J = 8.0$ Hz), 7.16 (m, 2H).

5-Phenyl-[1,3,4]oxadiazol-2-ylamine (**entry 9**).

The compound was obtained as a white solid. The MS gave the molecular ion (M+) 161. mp 245-248°C; ^{1}H NMR (DMSO-d$_6$): δ 7.50 (d, 2H), 7.32 (m, 3H), 7.20 (d, 2H).

[1,2,4]Triazolo[4,3-*a*]pyridin-3-ylamine (**entry 10**).

The compound was obtained as an off-white solid. The MS gave the molecular ion (M+) 134. mp 238-241 °C; ^{1}H NMR (DMSO-d$_6$): δ 8.65 (d, 1H), 7.80 (m, 1H), 7.33 (m, 2H) 6.90 (br, 2H).

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