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Metal free amination of 2-chloroazoles in aqueous medium

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ABSTRACT

A green approach for the synthesis of 2-amino azoles by the reaction of 2-chloro azoles with various types of amines using water as an environment friendly solvent at room temperature has been developed. The significant features of this methodology are short reaction time and easy product separation. This approach provides various biologically active compounds in good to excellent yields without adding any catalyst, ligand, or base.

During the last two decades, the importance of water as a benign solvent medium for organic synthesis has attracted considerable interest among the organic researchers.[1–4] Compared to common organic solvents, the unique and unusual physical properties of water such as high specific heat, high surface tension, high dielectric constant, amphoteric nature, large cohesive energy, density, and chemical properties such as the ability to form hydrogen bonds positively influenced the use of water in various chemical reactions.[5–7]

In synthetic organic chemistry, C–N bond formation has got more prominence due to the prevalence of amino groups in bioactive natural products.[8] C–N bond forming reactions are traditionally accomplished by Buchwald–Hartwig-type amination,[9] Ullmann,[10] Gold berg couplings,[11] and cross coupling reactions of Boronic acids, stannates, and siloxanes with corresponding amines.[12]

N–Hetero aryl compounds are common motifs in pharmaceutical research[13] as they resemble some of the biologically active molecules. 2-Amino benzoxazole/benzothiazole skeletons with piperazine substituent represent significant biological activities such as anticancer,[14,15] anti-microbial (**1**),[16] anti-inflammatory (**2**),[17] anti-HIV (**3**),[18] and for the treatment of Alzheimer's disease as well as schizophrenia (**4**).[19]

The related important biologically active structures are shown in Figure 1.

Several protocols for synthesizing 2-amino azoles have been developed in the past. Usually these azole derivatives are synthesized via aromatic nucleophilic substitution (SNAr) of amines with hetero aryl halides using various metal-base combinations catalyzed by Cu, Ag, Mn, Fe, Co, or Ni.[20–22] However, several of them are not recyclable, toxic, expensive, moisture sensitive, or environmentally not benign and required higher reaction temperatures. Due to some of the above disadvantages associated with the earlier methods, it prompted us to look into a novel, mild, and atom-economy method toward direct azole amination, which is economically viable and environmentally benign. In continuation of our earlier novel methodologies,[23,24] the present protocol for the synthesis of 2-*N*-substituted azoles via C–N coupling, offers a justification for all green chemistry principles (Scheme 1).

Initially, the amination of 2-chlorobenzothiazole (1.0 mmol) was investigated in H_2O as a solvent (2 mL) using 2 equiv of base under various reaction conditions. Among the different bases examined K_2CO_3 and K_3PO_4 afforded the expected products in trace amounts (Table 1, entries 1 and 2) and bases like Na_2CO_3 and Et_3N provided required coupled products in moderate yields (Table 1, entries 3 and 4). Other bases such as KOH and NaOH resulted in good yields (Table 1, entries 5 and 6). However, with LiO^tBu, the product was obtained in maximum yield (Table 1, entry 7). While studying different parameters of the process, it was observed that even in the absence of base the reaction proceeded completely to get excellent yields (Table 1, entry 8). It was observed that the increase in reaction temperature also did not have much effect (Table 1, entries 9 and 10). It was also observed that reactions with a small quantity of secondary amine (Table 1, entries 11 and 12)

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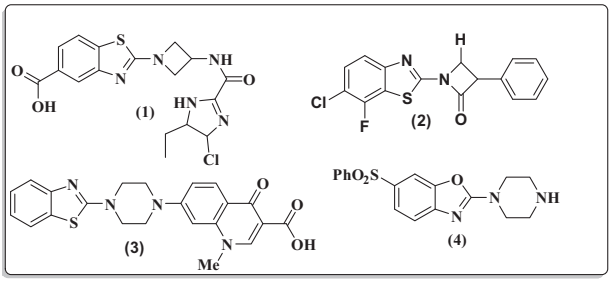


Figure 1. Biologically active compounds with 2-*N*-substituted azole structure.

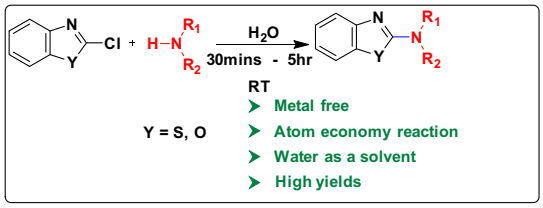
were not encouraging. Finally, we conducted reactions in polar organic compounds such as DMSO and DMF, which provided excellent yields (Table 1, entries 13 and 14) which are slightly higher than in the case of water as solvent (Table1, entry 8). Overall, in this exhaustive study of the parameters, it is concluded that the desired cross coupling product can be obtained when 2-chlorobenzothiazole (1.0 mmol) is added to the secondary amine (2.0 equiv) in the presence of water (2 mL) as a solvent at room temperature. The most advantageous point of this protocol is the purification process, in which the crude product in all piperazine reactions can be separated without column chromatography, by giving a simple wash with pure hexane followed by pet ether.

To explore the scope of the reaction, various amines are reacted with 2-chloroazoles under optimized reaction conditions and the results are summarized in Table 2.

This protocol was observed to be compatible with a broad range of aliphatic and cyclic amines with both benzoxazoles and benzothiazoles. Cyclic secondary amines such as pyrrolidine (**C**1, **C**2), piperidine (**C**3, **C**4), morpholines (**C**5, **C**6, **C**9), and azepane (**C**27) provided good yields. Several new compounds with interesting pharmacophores were also synthesized in good yields (**C**9, **C**14, **C**19, **C**20, **C**21). Aliphatic acyclic amines such as dimethyl (**C**28, **C**29), diethyl (**C**30, **C**31), and diisopropyl (**C**32) amines underwent smooth conversion to the desired products in moderate yields. From the above Table 2 it can be concluded that the reaction time for the formation of the product depends upon the nature of the secondary amines (cyclic/acyclic/nature of group on piperazine moiety).

Conclusion

In summary, to the best of our knowledge an environmentally benign and transition metal free protocol was developed for the first time for the amination of 2-chloro azoles using water only as a solvent medium. These reactions were performed using various types of amines to obtain products in moderate to excellent yields. The attractive and notable features of this green approach are high functional group compatibility, high yields, and eco-friendly aspects such as avoiding harmful organic solvents and toxic catalysts. This protocol may be useful for basic as well as industrial research.



Scheme 1. Amination of 2-chloro azoles.

Experimental section

General experimental procedure for the amination of 2-chlorobenzothiazole

The reaction was carried out in a 25 mL round bottom flask equipped with magnetic stir bar charged with 2-chlorobenzothiazole (1 mmol), aminating agent (2.0 equiv), and water (2 mL). The resulting reaction mixture was stirred at room temperature for 30 min to 5 h (varies with nature of the amine). The reaction progress was monitored by TLC. After the reaction, it was worked up with ethyl acetate. Crude product was purified by column chromatography (for piperazine derivatives column is not required). The identity and purity of the product was confirmed by ^{1}H NMR, ^{13}C NMR, and ESI-MS.

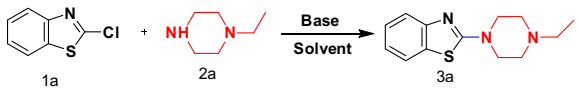
Representative experimental procedure for the synthesis of 2-(4-phenylpiperazin-1-yl)benzo[*d*]oxazole (C12)

2-Chlorobenzoxazole (1.0 mmol), phenyl piperazine (2.0 mmol), are taken in solvent (water-2 mL) and stirred at room temperature for 30 min. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was worked up with ethyl acetate (2 × 10 mL) and saturated brine solution, and dried over anhydrous Na_2SO_4. After the evaporation of ethyl acetate under reduced pressure, the crude product was washed with diethyl ether to give pure product. The identity and purity of the product were confirmed by ^{1}H, ^{13}C NMR and mass spectra.

Spectral data of 2-(4-phenylpiperazin-1-yl)benzo[*d*]oxazole (C12)

White solid (84%); mp 147–148 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.38 (d, J = 7.7 Hz, 1H), 7.33–7.22 (m, 3H), 7.18 (td, J = 7.7, 0.8 Hz, 1H), 7.04 (td, J = 7.9, 1.0 Hz, 1H), 6.98 (d, J = 8.0 Hz, 2H), 6.92 (t, J = 7.3 Hz, 1H), 3.99–3.65 (m, 4H), 3.40–3.16 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 162.1, 151.1, 148.8, 143.0, 129.3, 124.1, 116.9, 116.4, 108.8, 49.21, 45.6; ESI-MS: m/z 280 $[M+H]^+$.

Table 1
Optimization studies: Screening of various bases and solvents[a]



Entry	Solvent	Base (2 equiv)	Temp (°C)	Time (h)	Yield[b] (%)
1	H_2O	K_2CO_3	rt	3	Trace
2	H_2O	K_3PO_4	rt	3	Trace
3	H_2O	Na_2CO_3	rt	3	59
4	H_2O	Et_3N	rt	3	65
5	H_2O	KOH	rt	3	71
6	H_2O	NaOH	rt	3	75
7	H_2O	LiO^{t}Bu	rt	3	90
8	H_2O	—	rt	3	88
9	H_2O	—	80	3	89
10	H_2O	—	100	3	92
11	H_2O	—	rt	3	53[c]
12	H_2O	—	rt	3	68[d]
13	DMF	—	rt	3	91
14	DMSO	—	rt	3	92

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (2.0 mmol), base (2 equiv), solvent (2 mL).
[b] Isolated yield of the pure product.[8–14] Absence of base.
[c] Secondary amine (**2a**): 1.0 mmol.
[d] Secondary amine (**2a**): 1.5 mmol.