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Synthesis of 1,2 diamines under environmentally benign conditions: application for the preparation of imidazolidiniums

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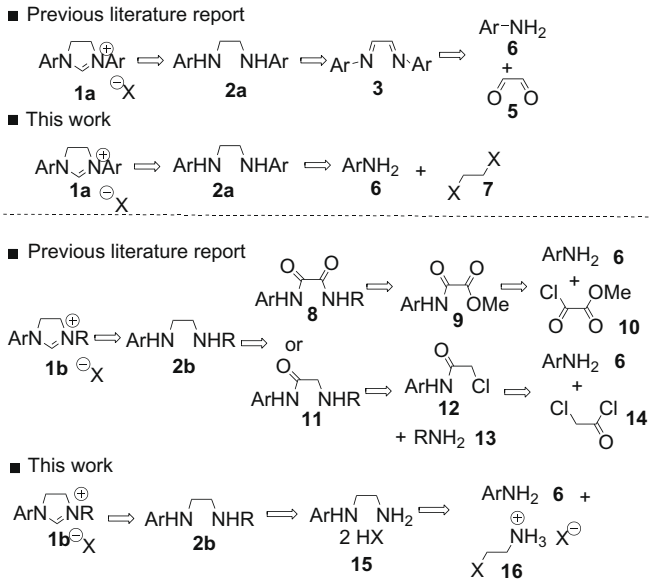
ABSTRACT

An environmentally friendly and economically attractive access to unsymmetrical and symmetrical 1,2-diamines has been developed. Chemoselective N-monoalkylation in water and alcoholic solvents was demonstrated. This method represents a simple and scalable preparation (2–3 steps) of symmetrical and unsymmetrical imidazolidinium salts, precursors of *N*-Heterocyclic Carbenes.

The replacement of classical organic solvents by environmentally friendly reaction media is of contemporary attention. Water and alcohols are ideally suited for industrial purpose due to their nontoxic character. Indeed, water has special characteristics which are not encountered with other solvents such as high thermal capacity, hydrophobic association, high polarity, and hydrogen-bonding ability.[1] Due to these properties, reactions in and 'on' water often show higher reaction rates, better selectivity and yields than those performed in classical organic solvents.[2]

Within the course of a research program in the field of metal-*N*-Heterocyclic Carbenes (NHCs) devoted to biological applications and click reaction catalysis,[3] a fast synthesis of various imidazolidinium cations was needed. NHCs, that constitute an important class of ligand for multiple catalyzed chemical transformations,[4] are generally obtained from their imidazolidinium precursors **1a–b**. The symmetrical imidazolidiniums **1a** are classically obtained in three steps: azadiene **3** formation from glyoxal **5** condensation with a primary amine **6** followed by reduction yielding 1,2-diamine **2a** and cyclization (Scheme 1).[5] The unsymmetrical imidazolidinium **1b** results from a sequential addition of two different amines (**6** and **13**) to methyl oxalyl chloride[6] **10** or chloroacetyl chloride[7] **14** followed by reduction to access to the unsymmetrical 1,2-diamine **2b** (Scheme 1).[8] In all cases, an oxidation level adjustment along the synthesis is needed. Unfortunately this step proved to be often problematic. We postulated that both symmetrical and unsymmetrical 1,2 secondary diamines **2a–b** could be accessed directly, avoiding any reduction step, from substitution on 1,2-dihalogenoethane **7** or halogenoethylammonium **15** by substitution reactions in one or two steps, respectively. We were then facing the challenging preparation of symmetrical and unsymmetrical 1,2-diamines **2a–b** in one or two steps, respectively.



Scheme 1. Symmetrical and unsymmetrical imidazolidiniums retrosynthesis.

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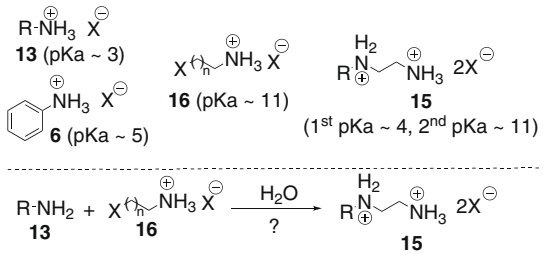
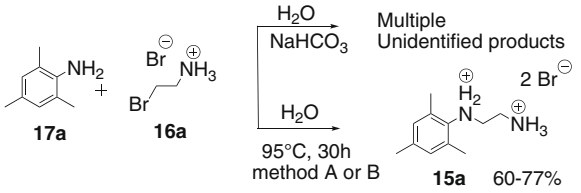


Scheme 2. Influence of pK_as on the N-monoalkylation of primary amines in water.

Generally, polyamines and 1,2-diamines,[9] which are of great importance in the chemical industry as basic and key intermediates, are obtained using harsh conditions or multistep sequences. Secondary or tertiary amines could be prepared by reductive amination,[10] amide reduction,[11] oxidative coupling,[12] hydroamination,[10h–j,13] or N-alkylation.[14] The last solution seemed to us the most attractive, considering the desired oxidation state, and therefore a shorter number of steps to prepare the final imidazolidiniums **1a** and **1b**. We are presenting in this letter, our efforts for the N-monoalkylation of amines in water and their further transformation into imidazolidiniums (Scheme 1).

An important drawback for the N-alkylation of amines is the formation of several polyalkylated/halogenated by-products, arising from multiple alkylation reactions, when alkyl halides are used. Recently, some strategies have emerged to solve this long standing problem of N-polyalkylation of primary and secondary amines using either basic conditions (pH controlled),[15] anhydrous cesium hydroxide,[16] or phase transfer catalysts.[17] Along these elegant reports and to the best of our knowledge, the direct N-monoalkylation of primary amines in water without any additive, taking advantage of pK_a difference between the primary amine (starting material: alkyl- or aryl-amine) and the secondary amine (product) has not yet been reported (Scheme 2).

The question was simple: could we N-monoalkylate the primary amine **13** and release the secondary ammonium salt **15** to avoid N-polyalkylation? Our plan consisted in comparing the reactivity of **6** (p$K_a \sim 5$) and other primary alkylamines **13** (p$K_a \sim 3$) with bromoethylammonium **16a** (p$K_a \sim 11$) under basic and neutral aqueous conditions (Scheme 3).[18] As expected, the reaction in the presence of base led to the formation of multiple unidentified side products, whereas the reaction in water produced the desired N-monoalkylated mesitylamine **15a** in 60% yield (Scheme 3). We suspected that the bromoethylamine generated under basic conditions could form the corresponding aziridine and multiple side products. As the inspection of pK_a values of N-monoalkylated ammonium **16** (p$K_a \sim 11$) and aniline **6** (p$K_a \sim 5$) has revealed that the proton exchange equilibrium is largely displaced toward the former, we assume that the hydrobromide salt could act as the protecting group for **16** and diamine **15** and would avoid the formation of side products. Consequently, using base free conditions in water, we were pleased to observe a selective N-monoalkylation of mesitylamine **17a** to provide the desired alkylated aniline **15a** in 60% yield.



Scheme 3. First result of N-monoalkylation in water. Method A: mesitylamine **17a** (1.0 equiv), bromoethylammonium **16a** (1.0 equiv), H_2O (1 M), 95 °C, 30 h (60% yield); Method B: mesitylamine **17a** (2.0 equiv), bromoethylammonium **16a** (1.0 equiv), H_2O (6 M), 95 °C, 18 h (77% yield).

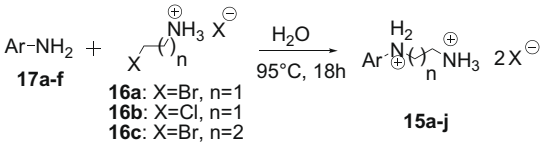
After numerous experiments, we noticed that 2 equiv of mesitylamine **17a** in more concentrated media (H_2O, 6 M) for a shorter reaction time (18 h) were the optimal conditions to obtain the desired N-monoalkylated product **15a** in 77% yield (Scheme 3, method B). Encouraged by these preliminary results, we decided to extend this efficient and simple method to a larger set of arylamines **17a–f** (Table 1). Our protocol consists in using 'on water' conditions; a layer of aniline **17a–f** (2.0 equiv) is stirred vigorously for 18 h at 95 °C, in the presence of a 6M solution of **11a–c** (1.0 equiv) in water. Simple extraction of the resulting solution allowed the recovery of unreacted anilines **17a–f**, whereas the desired products **15a–j** remained in the aqueous phase and could either be directly precipitated at 0 °C or concentrated to dryness and further crystallized from alcohol. The reaction proceeded well with mesitylamine **17a** regardless of the nature of the alkylating agent **16a–b** (Br or Cl) and the chain length **16c** (Table 1, entries 1–3). Aniline **17b** as well as *p*-isopropylaniline **17c** were also prompt to produce the corresponding N-monoalkylated products **15d**, **15e,** and **15f** in good yields with the various alkylating agents (Table 1, entries 4–6). The substitution in *para* position by chloro and acetamido groups did not affect the alkylation process, and products **15g–i** were obtained respectively in 51%, 58%, and 91% yield, respectively, (Table 1, entries 7–9). On the other hand, 2,6-diisopropylaniline **17f**, due to the high steric hindrance surrounding the nucleophilic center and/or for hydrophobic reasons was unreactive toward the different alkylating agents tested in water (Table 1, entry 10).

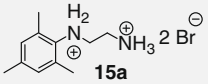
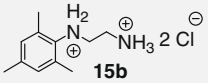
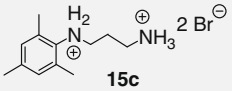
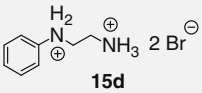
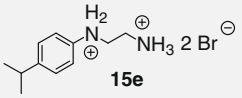
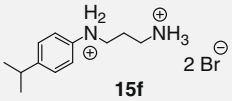
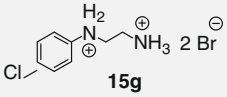
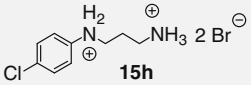
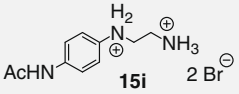
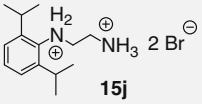
Kotschy and co-workers described the formation of N,N′-diarylated 1,2-diamines using Buchwald–Hartwig coupling or selective reductive amination (at the primary amine site) to introduce an arylmethyl moiety.[7b] Interested in the possible formation of fluorescent NHCs, we proposed the introduction of a pyrenyl moiety on an imidazolidinium precursor using a reductive amination reaction (Scheme 4).[3d] The N-monoarylated 1,2-diamine dihydrobromide salt **15a** was thus condensed with 1-pyrenecarboxaldehyde **18** generating an imine intermediate, which was reduced in situ with sodium cyanoborohydride to yield the unsymmetrical disubstituted 1,2-diamine. Further treatment with hydrochloric acid afforded the 1,2-diamine dihydrochloride salt **19**. Subsequent cyclization using the orthoester condensation procedure provided the desired unsymmetrical imidazolidinium **20**, in three steps and a 76% overall yield (Scheme 4**).**

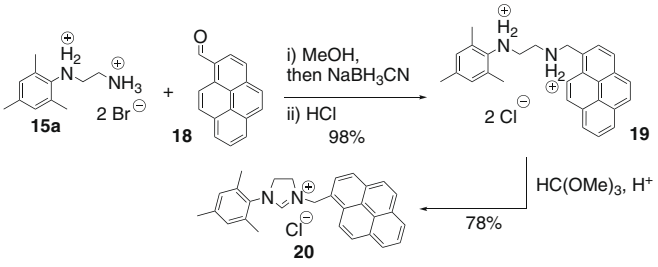
After demonstrating the applicability and efficiency of our N-monoalkylation in water, we examined the use of methanol, a solvent that allows a better solubilization of all reactants and a decreased reaction temperature, for the preparation of symmetrical N,N′-disubstituted 1,2-diamines **21** (Scheme 5).[20] We were pleased to observe that alkylation of mesitylamine **17a** with 1,2-dibromoethane **7** yielded the desired N,N′-diarylated 1,2-diamine dihydrobromide salt **21a** in 56% yield (unoptimized). As expected the N-alkylation of the hydrophobic adamantylamine proved to be more difficult and the corresponding 1,2-diamine dihydrobromide salt **21b** was isolated in a modest 38% yield. Both 1-naphthylamine and cyclohexylamine, less crowded substrates, furnished the desired 1,2-diamines **21c** and **21d** in 57% and 65% yield, respectively, as pure hydrobromide salts after a simple filtration.

The formic acid catalyzed cyclisation reaction with trimethylorthoformate completed the synthesis of the symmetrical imidazolidiniums **22a–c** in excellent yields (Scheme 6).[22] This new N-monoalkylation protocol of alkyl and aryl amines resulted in a two-step access to the common SIMes,HX imidazolidinium (1,3-bis-(2,4,6-trimethylphenyl-1-yl)-imidazolidinium) **22a**, and to the less-examined SIAd,HX (1,3-bis-(adamantyl)imidazolidinium))

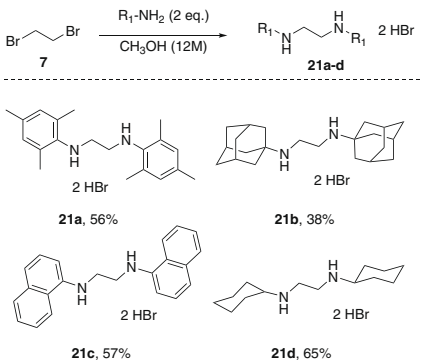
Table 1
Scope of the N-monoalkylation of arylamines in water[19]



Entry	Alkylating agent	Arylamine (Ar=)	Product	Yield (%)
1	**16a**	17a (C_9H_{11})	 **15a**	71
2	**16b**	17a (C_9H_{11})	 **15b**	70
3	**16c**	17a (C_9H_{11})	 **15c**	72
4	**16a**	17b (C_6H)	 **15d**	72
5	**16a**	17c (C_9H_{11})	 **15e**	58
6	**16c**	17c (C_9H_{11})	 **15f**	40
7	**16a**	17d (C_6H_4Cl)	 **15g**	51
8	**16c**	17d (C_6H_4Cl)	 **15h**	58
9	**16a**	17e (C_8H_8NO)	 **15i**	91
10	**16a**	17f ($C_{12}H_{17}$)	 **15j**	0



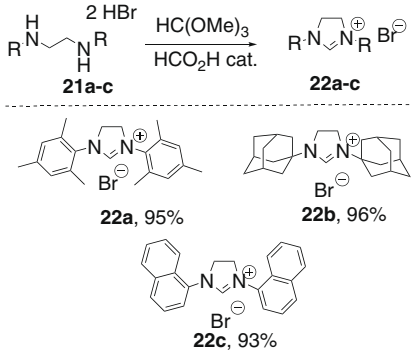
Scheme 4. Preparation of unsymmetrical imidazolidinium **20**.



Scheme 5. Preparation of symmetrical N-monoalkylated or arylated 1,2-diamines **21a–d**.[21]

22b and SINap,HX (1,3-bis(naphthalen-1-yl)-imidazolidinium) **22c**.[23] Notably, the preparation of SINap,HBr **22c** by the known azadiene method proved to be difficult and was achieved in the literature by a double Hartwig–Buchwald reaction. In our hands, the reaction of 1-naphthylamine with glyoxal resulted systematically in the formation of an untreatable black precipitate.

In conclusion, in this preliminary communication, we have presented a valuable access to unsymmetrical and symmetrical 1,2-diamines and unveiled primary amines reactivity for N-monoalkylation in water and methanol. This environmentally friendly protocol, which represents the most simple and scalable prepara-



Scheme 6. Two-step synthesis of symmetrical imidazolidiniums **22a–c.**

tion of these compounds in the literature, led to an efficient preparation of several symmetrical and unsymmetrical imidazolidinium salts in two or three steps. However, for unsymmetric compounds, our protocol is limited to derivatives bearing one aromatic substituent. We are currently studying the synthetic paths to get around such limitations; results will be published in due course.

Supplementary data

Supplementary data (procedures, copies of ^{1}H and ^{13}C spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.072.

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20. Ethanol and isopropanol were also tested but with poor success.
21. *Procedure for the preparation of (N,N′-dicyclohexyl) 1,2-ethanediamine dihydrobromide* **21d** *in alcoholic solvent*: Cyclohexylamine (20.0 g, 202 mmol, 3.0 equiv) and 1,2-dibromoethane (12.6 g, 67.0 mmol, 1.0 equiv) were sequentially added at room temperature to methanol (50 mL). The solution was vigorously stirred under reflux overnight. The solution was evaporated under reduced pressure to furnish a brown solid which was triturated with acetone (40 ml), filtrated, and washed with acetone to yield 16.7 g of compound **21d** as a white solid (65%).
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