RSC Advances

COMMUNICATION

View Article Online
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Cite this: *RSC Adv.*, 2014, **4**, 18229

Received 5th March 2014
Accepted 7th April 2014

DOI: 10.1039/c4ra01915f

www.rsc.org/advances

Selective *N*-alkylation of primary amines with R–NH_2·HBr and alkyl bromides using a competitive deprotonation/protonation strategy†

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Monoalkylation of primary amines using amine hydrobromides and alkyl bromides has been carried out. Under controlled reaction conditions the reactant primary amine was selectively deprotonated and made available for reaction, while the newly generated secondary amine remained protonated, and did not participate in alkylation further. Reaction was carried out under mild reaction conditions and was applicable to a wide range of primary amines and alkyl bromides.

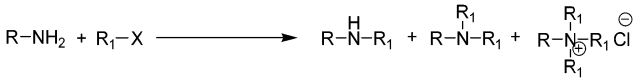
Amines are important because of their widespread application as synthetic intermediates[1] pharmaceuticals,[1] agrochemicals,[2] paints,[3] dyes,[4] drugs,[5] polymers,[6] *etc.* Development of synthetic approaches for selective mono-*N*-alkylation has been the focus of research for decades and it continues to be an active area of research, today also. Methods available for monoalkylation of amines includes reductive alkylation using aldehydes,[7] alkylation by alkyl halides[8] or their equivalents such as dialkyl sulfates or sulfonates[9] and alkylation by alcohols.[9,10]

Preparation of monoalkyl amines by amine–halide reaction is conceptually straightforward, reaction occurs under mild condition and numerous amines and halides are commercially available. But, in spite of its great potential it is rarely used for selective monoalkylation of amines. The limited synthetic applicability of this reaction stems from the fact that once alkylation of primary amine occurs, a secondary amine is generated which is more basic than primary amine. Now, the secondary amine also competes with primary amine for alkylation, and leads to formation of tertiary amine. Further alkylation of tertiary amine results in quaternisation of amine. Ultimately, a mixture of amines is obtained which renders the reaction of little synthetic importance (Scheme 1). Nevertheless, in view of the great scope of this reaction, efforts are being applied to make the reaction practically useful. Salvatore *et al.* have reported a procedure for monoalkylation of primary amine using cesium bases.[11] The selectivity was attributed to 'cesium effect' induced by cesium since exclusively; it was effective in comparison to other similar bases.

We wished to explore the potential of halide–amine reaction further with an aim to develop a milder, simpler, cost effective and general protocol for monoalkylation of primary amines. We reasoned that problem of over alkylation of amines may be resolved by exploiting the difference in basicity/nucleophilicity of primary/secondary amines. We hinged our approach on exploiting greater intrinsic basicity of secondary amine and thereby greater proton affinity in comparison to primary amines. Surprisingly, this simple approach has yet not been explored.

To accomplish this, we proposed to recruit halide salt of the amine and alkyl halide. We rationalized that under properly tuned reaction conditions, the reactant amine could be made available for reaction with the help of a suitable base, which preferentially deprotonates primary amine in the presence of secondary amine due to their difference in basicity. The halo acid formed during the reaction should remain bound to the newly generated secondary amine, driving it to its thermodynamic sink, RNH–R_1·HX and thereby preventing the secondary amine to participate in the reaction further.

Important considerations which could influence the fate of reaction to a great extent were; selection of suitable base and solvent for the reaction. For imparting selectivity, a non nucleophilic base with optimum basicity was essential: under the employed reaction condition it should deprotonate primary amine in preference to newly generated secondary amine (Scheme 2).



Scheme 1 Alkylation of amine with alkyl halide.

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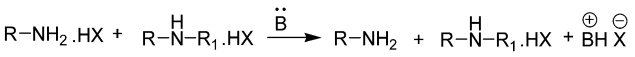
† Electronic supplementary information (ESI) available: General synthetic procedure, characterization data, ^{1}H and ^{13}C NMR spectra. See DOI: 10.1039/c4ra01915f



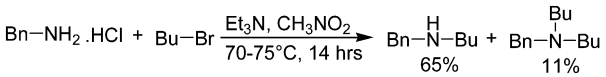
Scheme 2 Preferential deprotonation of primary amine.

Solvent often modulate basicity of amines: in aprotic solvents the basicity is governed by electronic factor of the amines and in protic solvent it is influenced by electronic factors as well as by degree of solvation.

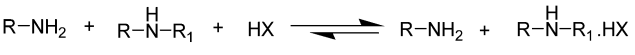
To see the feasibility of the concept, alkylation of benzylamine·HCl with butylbromide was attempted. Butylbromide and benzylamine·HCl were taken in nitromethane at 70–75 °C and one mole of triethylamine was added drop wise. Initially, good selectivity was obtained (5 h, 44% monoalkylation, 1% dialkylation, 55% unreacted primary amine) but, the reaction failed to progress further in the desired direction. After 14 h, 65% monoalkylated product was formed along with 11% dialkylated product, and 24% starting material remained unreacted. Formation of butylchloride retarded the reaction, and dialkylation was also observed (Scheme 3).

To explain this we presumed that since, primary requirement for selective monoalkylation was to prevent the reaction generated secondary amine from participating in the reaction by maintaining it in protonated form, hence, dialkylation may be due to incomplete protonation of secondary amine, and it may require some additional time to attain equilibrium between primary and secondary amine according to Scheme 4.

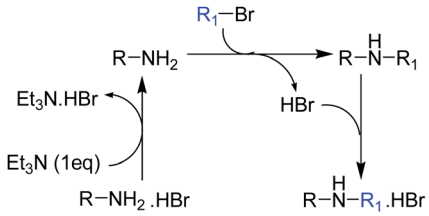
To evade formation of chlorobutane; hydrochloride salt of the amine was replaced by hydrobromide salt and triethylamine was added in portions at regular intervals to avoid over-alkylation. After each addition (triethylamine), reaction was allowed to undergo complete reaction in terms of alkylation of the available free primary amine, and establishment of equilibrium in the reaction mixture according to Scheme 5. With



Scheme 3 Alkylation of benzylamine hydrochloride with butylbromide.



Scheme 4 Equilibrium between protonated primary and secondary amine.



Scheme 5 Selective mono alkylation of amines.

these modifications, gratifying results were obtained entry 1 Table 1.

Next, various solvents were screened for their applicability in this reaction. Both protic and aprotic solvents such as ethanol, THF, DMF, toluene, DMSO, acetonitrile, *etc.* were investigated. In THF, acetonitrile and toluene reaction did not occur satisfactorily mainly due to the insolubility of the amine salt. In ethanol the progress of the reaction was very slow. Reaction in DMSO also showed good selectivity but satisfactory yield was not found. In DMF the reaction was progressed well but, simultaneous formylation of amine was also observed. To reduce formylation, reaction was carried out at 20–25 °C.

We were pleased to notice that lowering temperature prevented the side reaction without retarding the rate of desired reaction considerably. Inclusion of drying agent like molecular sieve 4 Å enhanced both the rate of *N*-alkylation and selectivity. Conducting the reaction in DMSO also produced good results, but considerable loss in the yield during work up was observed, hence DMF was finally selected (Table 1).

After solvent screening, we directed our attention towards optimization of the base. Various candidate amine such as pyridine, diisopropylethylamine (DIPEA), *N*,*N*-dimethyl-4-aminopyridine (DMAP), 1,8-diazabicycloundec-7-ene (DBU), dicyclohexylamine (DCHA), collidine were studied (Table 2). DIPEA and DMAP produced slightly better results in terms of selectivity but their removal from the reaction mixture was found to be difficult in comparison to triethylamine. Weaker

Table 1 *N*-Alkylation of benzylamine·HBr with *n*-butylbromide in different solvents[a]

Solvent	Temperature (°C)	Selectivity	Time (h)	Yield
Nitromethane	70–75	80 : 20	10	70
Ethanol	Reflux	4 : 0	10	—
DMF	20–25	87 : 9	9	76
DMSO	20–25	90 : 7	9	65
THF	20–25	—	—	—
Toluene	20–25	—	—	—
Acetonitrile	20–25	—	—	—

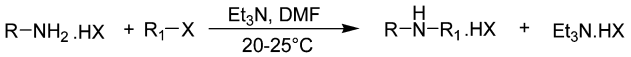
[a] Reactions were carried out with benzylamine·HBr (1 eq.), *n*-butylbromide (1.1 eq.) and triethylamine (1 eq.).

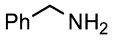
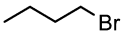
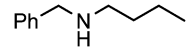
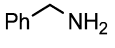
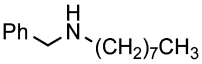
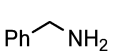
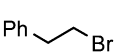
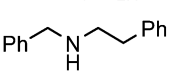
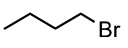
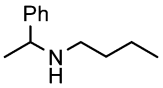
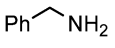
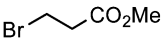
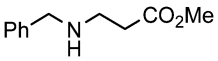
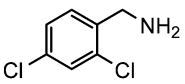
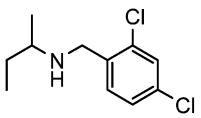
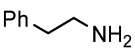
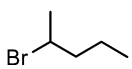
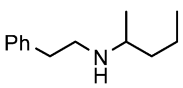
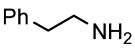
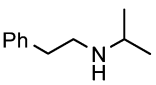
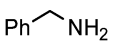
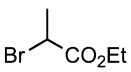
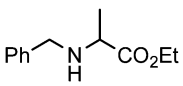
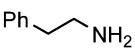
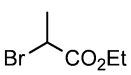
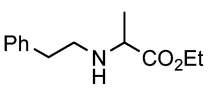
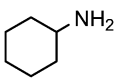
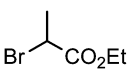
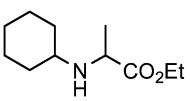
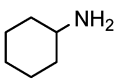
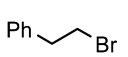
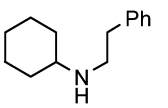
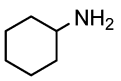
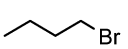
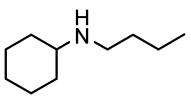
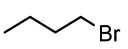
Table 2 *N*-Alkylation benzylamine·HBr with butylbromide utilizing different bases[a]

Base	Selectivity	Time	Yield
Pyridine	—	—	—
Triethylamine	87 : 9	9	76
DIPEA	89 : 8	8	77
DMAP	93 : 4	8	79
DBU	81 : 16	6	73
DCHA	83 : 13	6	74
Collidine	37 : 0	6	—

[a] Reactions were carried out with benzylamine·HBr (1 eq.), *n*-butylbromide (1 eq.) in DMF at 20–25 °C.

Table 3 Chemoselective formation of secondary amines from primary amines and alkyl halides



Entry no.	Primary amine·HBr	Alkyl halide	Product	Et_3N eq.	Time (h)	Selectivity[b]	Yield[c]
1				1	9	87 : 9	76
2		*n*-C_8H_{17}-Br		1	9	81 : 15	73
3				1	10	86 : 10	78
4				1	10	87 : 6	79
5				1	16	85 : 12	77
6[a]				3	12	100 : 0	82
7[a]				3	11	100 : 0	87
8[a]				3	11	100 : 0	86
9				1	12	92 : 0.2	84
10				1	10	96 : 0.5	83
11				1.2	22	73 : 0.3	62
12				1.2	18	77 : 1	64
13				1	16	93 : 3	76
14	Ph-NH_2			1.5	15	70 : 10	63
15		CH_3-$(CH_2)_4$-Br		1.5	10	71 : 8	66

[a] Free amine was used. [b] Selectivity – monoalkylation : dialkylation, reaction was monitored by GC-MS, rest of the primary amine remained unreacted. [c] Isolated yield.

base like pyridine as expected were found ineffective, collidine also did not produce satisfactory conversion. Application of inorganic bases was also not found effective. Keeping in view the practical applicability, triethylamine remained the base of choice.

An optimized procedure utilizing hydrobromide salt of benzylamine, butylbromide, triethylamine and DMF follows as: 1 mmol of amine hydrobromide salt, 1.1 mmol of butylbromide and 0.25 g of 4 Å molecular sieves were taken in 1 ml dry DMF at 20–25 °C. Triethylamine 1 mol, was mixed with 1 ml of DMF and added to the reaction mixture portionwise (1/40th) over a period of 8 h with continuous stirring. Progress of the reaction was monitored by TLC and GC-MS. On completion of the reaction monoalkylated product was isolated by usual work up procedure.

With the optimized reaction conditions in hand, scope of this strategy was probed with a variety of amines and alkyl bromides. *N*-Alkylation of all the primary amine with primary halide investigated in this work progressed smoothly (Table 3, entry 1–4). Next, the protocol was attempted for secondary halides. In case of cesium promoted *N*-alkylation of amines, secondary halides have been reported to take longer reaction times and additionally higher molar ratio of the halides (five folds) were required to yield the desired products.[11]

When reaction of secondary halides such as 2-bromobutane with 2,4-dichlorobenzylamine was attempted no appreciable conversion was found to occur until three equivalent of triethylamine were consumed. Under these conditions both the primary and as well as the secondary amine could be deprotonated, resulting in over alkylation. But, no over alkylation was observed and the selectivity was maintained, though the reaction occurred slower. We reasoned that selectivity might have been induced by the steric imposition of 2-bromobutane and no additional reagent may be required except a proton scavenger for the progress of the reaction. To confirm this we conducted the reaction with free 2,4-dichlorobenzylamine and 2-bromobutane in the presence of triethylamine. As expected, the reaction proceeded with same order of selectivity with no over alkylation (entry 6). All the mono functionalized sec. halide utilized in this reaction responded in the similar way (entry 6, 7, 8) which indicated that selectivity of alkylation was greatly influenced by the steric constraints. To investigate the role of solvent in inducing the selectivity, the reaction of 2-bromobutane and 2,4-dichlorobenzylamine was carried out under neat condition, without any solvent. Interestingly, most of the reactant remained unreacted, and a very marginal conversion (5%) was observed even after long hours of reaction. Carrying out the reaction in ethanol at reflux for long hours also did not improve the fate of the reaction. A probable explanation for this observation may be that reaction of primary amine with primary halide is following a S_N2 mechanism, while *N*-alkylation with secondary halides is proceeding with S_N1 mechanism. Since, secondary carbocations in S_N1 mechanism are stabilized by polar aprotic solvents; the reaction is being assisted by polar aprotic solvent.

The steric impositions were helpful in imparting selectivity only in limited cases. Reaction of activated secondary halides such as α-halo ester with free benzylamine failed to produce selectivity. But, useful outcome of the reaction was restored by employing of hydrobromide salt of benzylamine (entry 9). Similarly, good selectivity was observed in case of alkylation of phenylethylamine hydrobromide with 2-bromopropionate (entry 10). Reaction of cyclohexylamine with alkyl bromides and α-halo ester also exhibited excellent selectivity (entry 11, 12 and 13) but longer reaction time (22 h) was required. To investigate the scope the reaction further, aromatic amine was investigated (entry no. 14 and 15) and by employing a slightly higher amount of base, they were also found to be suitable partners in this reaction.

In conclusion, we have demonstrated a simple and efficient approach for monoalkylation of primary amines. Due to easy availability of a broad range of substrates, convenience and practicability of the method, this may find wide application in synthetic and medicinal chemistry.

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