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Selective Hofmann alkylation of aromatic-aliphatic diamines in the presence of carbon dioxide

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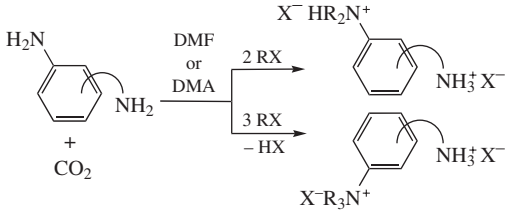
Selective Hofmann alkylation at arylamino group in carbon dioxide medium was demonstrated on model diamines containing aliphatic and aromatic primary amino groups, namely, 2-$H_2NC_6H_4CH_2NH_2$, 3-$H_2NC_6H_4CH(Me)NH_2$, and 4-$H_2NC_6H_4CH_2CH_2NH_2$. Depending on the spatial factors, di- or trialkylarylammonium derivatives are selectively formed in amide solvents (DMF, DMA) without additional base.

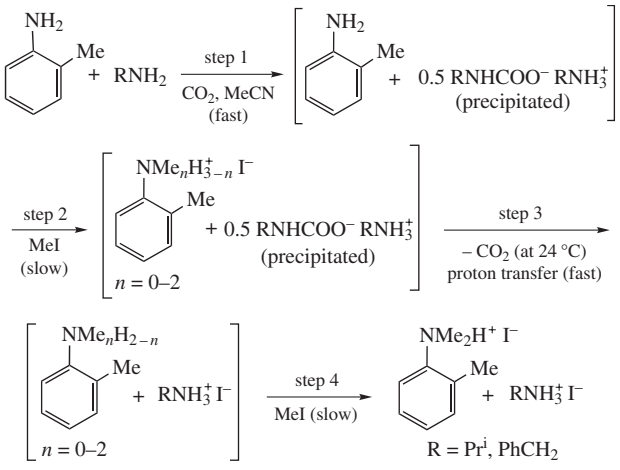


The use of various protecting groups is a common practice in the chemistry of organic amines. In the context of green chemistry, the employment of the reversible reactions of CO_2 with amines for *in situ* temporary protection is preferable. Nevertheless, the number of works in which this strategy is implemented is rather small and includes the reactions with 'soft' reagents that are unable to break the rather labile RR′N–COOH bond.[1,2] For instance, acylation of (4-aminomethylphenyl)methanol with isopropenyl acetate in the presence of CO_2 leads to the selective modification of alcohol group.[1(*d*)]

Herein, we report on employment carbon dioxide for temporary protection of the alkylamino group in the selective alkylation of diamines containing both aliphatic and aromatic amino groups, when CO_2 blocks the strongly basic $AlkNH_2$ group so that only the less active $ArNH_2$ group undergoes alkylation. Depending on the steric factor, such alkylation proceeds selectively to form a single di- or trialkylated product of the arylamino group, as distinct from the classic non-selective Hofmann N-alkylation. The reaction of the diamine with more than two equivalents of the alkylating reagent without an additional base seems unlikely. However, in amide solvents such as DMF or *N*,*N*-dimethylacetamide (DMA), the reaction proceeds further, giving in the absence of steric hindrance an exhaustive alkylation product.

The possibility of the selective alkylation of an arylamino group in the presence of an alkylamino one in a CO_2 atmosphere was initially studied for methylation of model 1 : 1 mixtures (2-Me-$C_6H_4NH_2$/Pr^iNH_2 and 2-$MeC_6H_4NH_2$/$PhCH_2NH_2$) with MeI in MeCN. For the selective formation of a dialkylarylammonium salt from 2 equiv. of an alkyl halide, the low rate of quaternization is a prerequisite. Otherwise, the reaction mixture could contain four products due to similar basicity values of the substituted amino groups (Table S2, see Online Supplementary Materials) causing proton exchange. Preliminary experiments on the methylation of *o*-, *m*- and *p*-toluidines with an excess of MeI in MeCN showed that the $ArN^+Me_3I^-$ quaternary salt did not form only in the case of sterically hindered *o*-toluidine, whereas *m*- and *p*-toluidines gave mixtures of four salts. At the same time, the alkylation of *m*-toluidine with EtBr stopped when salt $ArN^+Et_2HI^-$ was formed, however, the reaction rate was lower. Therefore, the methylation of mixtures of *o*-toluidine and alkylamine was the model reaction of choice. In the absence of carbon dioxide, the alkylation of model mixtures proceeds unselectively and leads to a mixture of seven products: 3 for $ArNH_2$ and 4 for $AlkNH_2$. The amount of MeI consumed, regardless of its excess, is limited by the number of amino groups.

Methylation of model mixtures in the presence of carbon dioxide were carried out at 60 bar (with or without liquid CO_2) or 1 bar.† In all cases, the reaction proceeds completely within 24 h with ~90% selectivity. Reaction at 1 bar CO_2 requires cooling of the reaction mixture down to ~ –15 °C at the initial stage of the process to achieve high selectivity. We believe that methylation in the presence of CO_2 involves four steps (Scheme 1). After the aliphatic amine is trapped in the form of ammonium carbamate[3] and precipitates (step 1) only one equivalent of MeI reacts (step 2). The subsequent methylation is possible only after liberation of CO_2 and recovery of the aliphatic amine (steps 3, 4). The aliphatic amine, due to its much higher basicity as compared to *o*-toluidine and its *N*-methyl derivatives, is converted to an



Scheme 1 *Reagents and conditions*: CO_2 (60 bar/24 °C or 1 bar/–15 °C), MeCN.

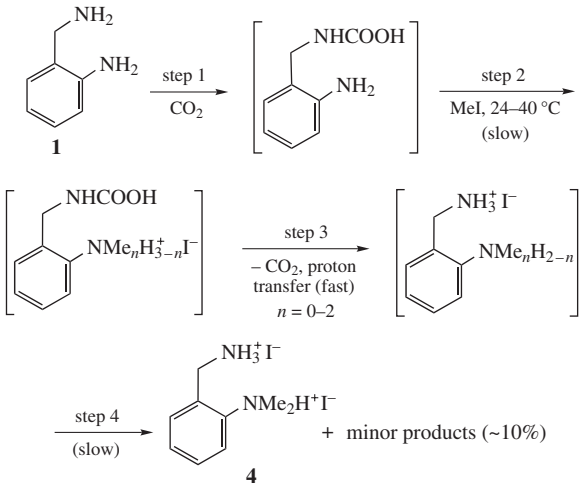
† For details of experiments and NMR spectra, see Online Supplementary Materials.

ammonium salt that does not participate in further processes. Thus, the by-products of methylation of the aliphatic amino group (for strictly equimolar mixtures of amines) can be formed only in step 2, *i.e.* before the complete consumption of the first equivalent of MeI. The proposed step sequence was proved by reacting two crude materials obtained independently, namely, methylated 2-$MeC_6H_4NH_2$ and carbamine derivative of $PhCH_2NH_2$. The result of this reaction was the same as in the case of 'one-pot' process.

The main experiments were carried out for model diamines, namely, 2-$H_2NC_6H_4CH_2NH_2$ **1**, 3-$H_2NC_6H_4CH(Me)NH_2$ **2**, and 4-$H_2NC_6H_4CH_2CH_2NH_2$ **3**. In the absence of carbon dioxide, their reactions with MeI in MeCN proceeded unselectively and led to mixtures of products (up to 16 compounds). In particular, alkylation of diamine **1** gave a mixture of 12 ammonium salts since the steric hindrance in **1** prevents exhaustive methylation of arylamino group. Compared with model mixtures of alkyl- and arylamines, alkylation of diamines **1**–**3** in MeCN in the presence of CO_2 has a very important difference. In the former case, alkylammonium carbamate precipitates, while the soluble aromatic amine is alkylated, *i.e.*, the slow stage of this reaction is homogeneous. In the case of diamines, this stage becomes heterogeneous due to the complete insolubility of ammonium carbamate, resulting in the unpractically prolonged reaction time.

It is known that the products of the reaction of aliphatic amines with carbon dioxide, depending on the solvent, can be either carbamic acids or ammonium carbamates (or a mixture thereof),[3] *e.g.*, α- and ω-(1-naphthyl)alkylamines in DMSO, DMF and pyridine are quantitatively converted into soluble carbamic acids.[4] In THF or dioxane, mixtures of carbamic acid and ammonium carbamate would form, while in C_6H_6, $CHCl_3$, MeCN, MeOH or Pr^iOH, the only products are poorly soluble ammonium carbamates.[4(b)] Unlike DMSO and pyridine, amide solvents do not react with alkylating agents; therefore, DMF and DMA were the solvents of choice for the alkylation of diamines **1**–**3** in the presence of CO_2.‡

Methylation of diamine **1** with an excess of MeI in DMF or DMA at 10–60 bar CO_2 resulted in the expected dimethylammonium derivative **4** (Scheme 2) with high selectivity (~90%). The main by-product, as in the case of model mixture of amines, was the monomethylation product of the aliphatic amino group. The methylation in DMF for 72 h at ambient temperature did not occur completely, anyway, more than 1 equiv. of MeI was consumed within this time. Reaction completion requires additional 72 h and can proceed in the absence of CO_2 without loss of selectivity. Attempts to accelerate the reaction by heating (45–60 °C) led to the formation of a completely insoluble (even in DMSO) precipitate. Compared with DMF, the reaction in DMA is slightly faster. Note that raising the pressure of CO_2 decelerates the reaction (the maximum rate was observed at 10 bar). Apparently, this fact is associated with the dependence of the carbamic acid decomposition rate on the concentration of CO_2 (see Scheme 2, step 3). However, CO_2 pressure of 1 bar is insufficient to provide good selectivity.



Scheme 2 *Reagents and conditions*: CO_2 (10–60 bar), DMF or DMA, 24–40 °C.

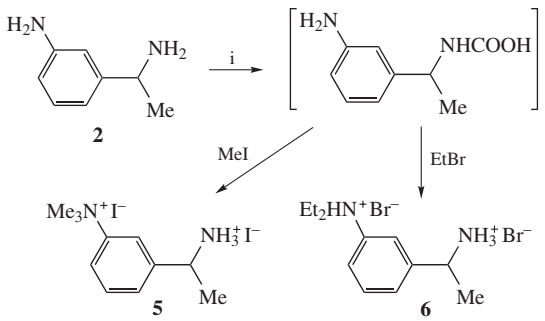
‡ Our data on the interaction of diamines with CO_2 in DMSO and DMF are in good agreement with the known data. These results will be published elsewhere.

Methylation of diamine **2** with an excess of MeI in DMA at a pressure of CO_2 of 60 bar led to unexpected results. Instead of a mixture of four ammonium salts $ArN^+Me_nH_{3-n}I^-$ (n = 0–3), the major product (92%) was a quaternary ammonium salt **5** (Scheme 3). Thus, more than 2 equiv. of MeI react without any additional base. This fact can be explained by the increase in the acidity of the arylammonium salts and simultaneous amide solvent-promoted decrease in the liberating HHal acidity. As a result, an aromatic amine capable of undergoing further alkylation is constantly present in the solution in a small steady-state concentration. For DMSO solutions, so it is (see, *e.g.*, the pK_a values of HBr and $PhNMe_2H^+$ presented in Table S2, Online Supplementary Materials). It is also known that the pKa values of weak acids in DMF are 0.5–1.5 units higher than those in DMSO.[5] DMA in this respect, apparently, occupies an intermediate position between DMSO and DMF. Similar results were obtained earlier for the exhaustive methylation of primary aliphatic and aromatic amines with MeI in DMF in the presence of 2 equiv. 4-hydroxy-2,2,6,6-tetramethylpiperidine and in its absence. Unlike aliphatic amines, 4-aminobenzoic acid and 3-nitroaniline give the corresponding quaternary ammonium salts in the absence of a base in significant yields.[6]

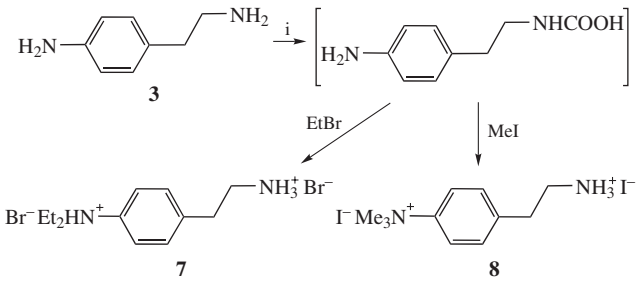
For better rationalization, we carried out model experiments on the methylation of *o*-, *m*- and *p*-toluidines with an excess of MeI in MeCN, DMF and DMA. In contrast to the reactions in MeCN, the final methylation products in the amide solvents were 2-$MeC_6H_4N^+HMe_2I^-$ and 3-, 4-$MeC_6H_4N^+Me_3I^-$, respectively. The reaction rate in DMA was noticeably higher than that in DMF (Table S1, Schemes S1–S3, Figures S2–S13, see Online Supplementary Materials). Thus, the exhaustive alkylation of aromatic amines in amide solvents does not require application of additional base and can be a real alternative to the known methods for the synthesis of quaternary arylammonium salts.[7]

Similar alkylation of diamine **2** with less reactive EtBr led to the expected diethylammonium derivative **6** (Scheme 3) with ~90% selectivity, the $ArN^+Et_3Br^-$ quaternary salt having not formed. The main by-product was the monoethyl derivative of the aromatic amino group, and the reaction time was much longer as compared to methylation.

Unlike substrates **1** and **2**, alkylation of diamine **3** may be carried out at elevated temperatures (55–60 °C), which significantly reduces the reaction time (Scheme 4). This is probably



Scheme 3 *Reagents and conditions*: i, AlkHal (6 equiv.), DMA, CO_2 (60 bar), 37 °C, 48 h (for MeI) or 144 h (for EtBr).



Scheme 4 *Reagents and conditions*: i, EtBr (4 equiv.) or MeBr (6 equiv.), DMA, CO_2 (60 bar), 52–55 °C, 72 h (for EtBr) or 55 h (for MeI).

due to the impossibility of the formation of a stable benzyl cation capable of initiating side processes during the reaction. The CO_2 pressure of 60 bar is sufficient for the alkylamino group protection. Ethylation of diamine **3** in DMA with an excess of EtBr under these conditions gave the corresponding diethyl derivative **7** with a selectivity of 93%. Just as for **6**, the main by-product was the monoethyl derivative of the aromatic amino group. Exhaustive methylation of **3** in DMA with an excess of MeI under similar conditions almost quantitatively resulted in the trimethylammonium salt **8** (see Scheme 4).

Salts **4**–**8** were isolated from reaction mixtures by precipitation with an excess of MeCN in moderate to high yields and were characterized by NMR and elemental analysis.[§]

In summary, the employment of carbon dioxide for temporary protection of the aliphatic amino group allows one to perform selective Hofmann alkylation of the aromatic amino group in diamines with both types of amino groups. This approach does not require additional steps for the introduction and removal of the protecting group and can be used for the selective synthesis of di- or trialkyl derivatives of the arylamine moiety by changing the steric factor. It is likely that the method can also be applied to the alkylation of polyamines with more than two amino groups (provided that the number of alkylamino groups does not exceed the amount of arylamino groups). The use of amide solvents (preferably DMA) for the exhaustive alkylation of aromatic amines without aliphatic amino groups may be helpful in some cases since no additional base is required.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.07.028.

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[§] To the best of our knowledge, only relative dihydrochlorides 4-R_2HN^+-$C_6H_4CH_2CH_2N^+H_3 \cdot 2\,Cl^-$ (R = Me, Et) are reported.[8]