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Selective Fmoc and Cbz protection of aromatic amino group in the presence of similar aliphatic function in liquid CO_2

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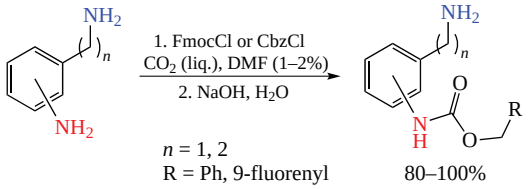
The selective protection of an aromatic amino group in the presence of aliphatic amino group in diamines by the action of FmocCl or CbzCl using liquid CO_2 as the solvent has been proposed. The developed method is preparative, does not require complex purification of the product, and meets the principles of green chemistry.



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Selective protection and deprotection of polyfunctional molecules is an important part of modern organic synthesis. In particular, for the synthesis of polyfunctional organic compounds containing several reactive groups of a similar nature, such as primary alkyl and aryl amines, the problem of their regioselective protection comes to the fore.[1–3] Various diamines containing both aniline and aliphatic amino groups are common precursors in the synthesis of chelators,[4,5] heteromacrocycles,[6] physiologically active[7] and natural compounds.[8] To date, a large number of protecting groups suitable for the preparation of protected amines are used in synthetic practice, but preparative approaches to monoprotected diamines are still scarce. A small number of works are devoted to the selective protection of more active, secondary amino groups in the presence of less active primary amino groups.[9,10] However, the most difficult task is still to create a protective group for a less active amino group in the presence of a more active one within one molecule. The classical approach using orthogonal protecting groups followed by deprotection of the more active amino group requires at least three consecutive reactions, which markedly reduces its productivity.[11]

The methods for obtaining *N*-(4-aminomethylphenyl)-acetamides by the action of acetic anhydride in aqueous solution of (4-aminobenzyl)amine in the presence of inorganic acids at different pH are known,[12,13] however, all of them either give a low yield of the desired product or are associated with difficulties in its isolation (separation from the starting materials and diacylated byproducts). To improve the yield of target *N*-(4-aminomethylphenyl)-containing amides, a one-pot method for preparation of the described monoprotected diamines was developed.[14] Regioselectivity was achieved by carrying out the reaction in 5% acetic acid in which the aliphatic amino group is protonated, while the basicity of the aniline amino group is not enough to react with acetic acid. The yields of the desired monoacylated products were close to 98%, however, to obtain 300 mg of the product, the use of 40 ml of a solvent (a mixture of dioxane, water, and acetic acid) was required.

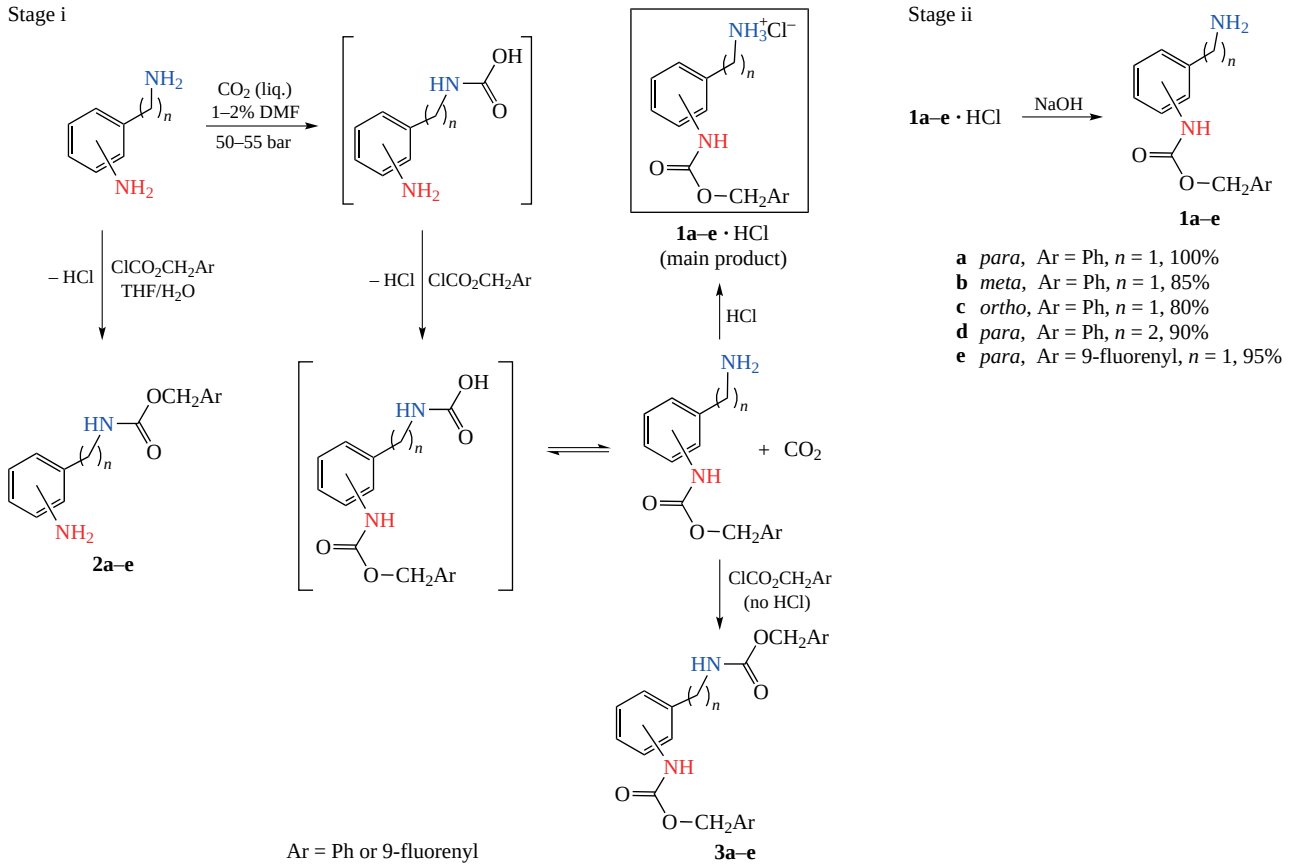
In this research, we propose a convenient alternative method for the synthesis of *N*-(4-aminomethylphenyl)-containing amides from the corresponding diamines. This method uses liquid CO_2, which acts both as a solvent and a reagent for introduction of a temporary carbamic protecting group for an aliphatic NH_2 group in the presence of an aniline. The proposed synthetic approach does not require the preparation of solvent mixtures or the use of acids and large amounts of organic solvents, and also has high 'atom economy', whereby it meets the principles of green chemistry.

Previously,[15] we have shown that (aminobenzyl)amines and (aminophenyl)ethylamines during the interaction with liquid CO_2 selectively form carbamic acid derivatives exclusively with the participation of the aliphatic amino group, which allowed their regioselective alkylation with iodo- and bromoalkanes. Extending this methodology to reactions with chloroformates such as CbzCl and FmocCl we have successfully herein obtained monoacylated products **1a**–**e** in high yields (Scheme 1).†

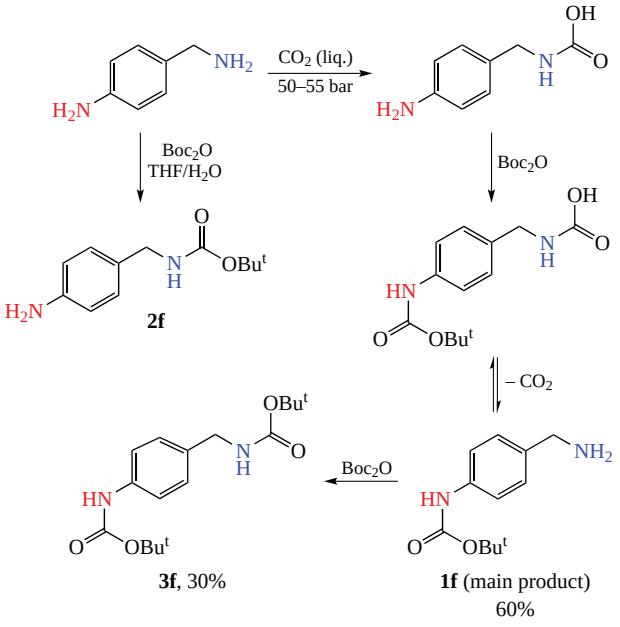
It was found that an important factor affecting the regioselectivity of the process is the formation of hydrogen chloride as a protic acid in the course of the acylation. The role of the liberated HCl seems to be the protonation of the free aliphatic amino group giving salts **1a**–**e**·HCl, which are in the equilibrium with carbamic acid in the CO_2 medium (see Scheme 1). This should lead to an increase in the regioselectivity of the reaction and the prevention of the formation of diacylated byproducts of type **3**.

This assumption is confirmed by the experiment with Boc_2O which does not form a strong acid as a secondary product in the course of acylation. When it was reacted with (4-aminobenzyl)-amine, besides the main product **1f**, diacylated compound **3f**,

† *Typical procedure*. Diamine (2.5 mmol) and DMF (1 ml) were placed into the reactor, and the reactor was filled with liquid CO_2 (50 ml) at a pressure of 50–55 bar. Reagent CbzCl or FmocCl (2.5 mmol) was placed into the injector, and the injector was filled with liquid CO_2 at the same pressure. The reactor was cooled in an ice water bath until the pressure was reduced to 40 bar, after which the acylating agent was transferred due to the pressure difference that appeared in the system. The cooling bath was removed and stirring was continued for 24 h. After the excess CO_2 pressure was released, the reaction mixture was washed from the reactor with water, treated with 1 M NaOH to adjust pH to 8, and extracted with diethyl ether. The extract was washed with water, brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure.



Scheme 1 *Reagents and conditions*: stage i, CbzCl or FmocCl, room temperature; stage ii, NaOH (1 M aq.).



Scheme 2 *Reagents and conditions*: Boc_2O, room temperature.

analogue of compounds **3a–e**, was formed in 30% yield (Scheme 2).

To study the scope and substrate limitation of the method, the reactions of 2-, 3-, 4-aminobenzylamines and 2-(4-aminophenyl)ethylamine with CbzCl, as well as (4-aminobenzyl)amine with FmocCl and Boc_2O in liquid CO_2 and, for comparison, in a 1:1 THF/water mixture (model conditions without the participation of CO_2) were carried out (see Scheme 1). In the absence of CO_2, the acylation reaction, as expected, proceeds predominantly at the more nucleophilic aliphatic amino group, however, the regioselectivity is low: in almost all cases, mixtures of products of mono- and diacetylation of starting diamines are formed in a ratio of 1:10 to 1:2 (Table 1, entries 2, 4, 6, 8, 10, 12). The ratios of the products were determined after chromatographic separation of mixtures.

During the optimization of reaction conditions in liquid CO_2, it was found that the reaction proceeded faster when 1% of co-solvent is added to the reaction mixture. The optimal co-solvent that improves the solubility of carbamic acids in liquid CO_2 and thereby accelerates the reaction, as in the case of alkylation of the described diamines,[15] was DMF. The amount of co-solvent required for the reaction does not exceed 1.0–1.5 ml of DMF per 2.5 mmol of the initial diamine and 50 ml of liquid CO_2.

The highest yields of target products **1a–e** (80–100%) were achieved by carrying out the reaction at CO_2 pressure of

Table 1 Acylation of aryl alkyl diamines in liquid CO_2 and in THF/H_2O mixture.

Entry	Diamine	Reagent	Solvent	Products (ratio)
1	(4-aminobenzyl)amine	CbzCl	CO_2[a]	**1a**
2	(4-aminobenzyl)amine	CbzCl	THF/H_2O	**2a**, **3a** (1:10)
3	(3-aminobenzyl)amine	CbzCl	CO_2	**1b**
4	(3-aminobenzyl)amine	CbzCl	THF/H_2O	**2b**, **3b** (3:1)
5	(2-aminobenzyl)amine	CbzCl	CO_2	**1c**
6	(2-aminobenzyl)amine	CbzCl	THF/H_2O	**2c**
7	2-(4-aminophenyl)ethylamine	CbzCl	CO_2	**1d**
8	2-(4-aminophenyl)ethylamine	CbzCl	THF/H_2O	**2d**, **3d** (3:7)
9	(4-aminobenzyl)amine	FmocCl	CO_2	**1e**·HCl[b]
10	(4-aminobenzyl)amine	FmocCl	THF/H_2O	**2e**
11	(4-aminobenzyl)amine	Boc_2O	CO_2	**1f**, **3f** (2:1)
12	(4-aminobenzyl)amine	Boc_2O	THF/H_2O	**2f**, **3f** (2:1)

[a] In all reactions in liquid CO_2, DMF (1–2%) was added as a co-solvent. [b] Free amine **1e** is poorly soluble for characterization.

50–55 bar, at room temperature for 24 h. The acylating agent was injected into the reactor by a CO_2 flow under high pressure. The main impurity found in the reaction mixtures in all cases was the initial unreacted diamine, and the amount of acylation by-products of types **2** and **3** did not exceed 5%. Purification of the target product **1a**–**e** was achieved by a single recrystallization from ethanol. Thus, the use of carbon dioxide for temporary protection of the aliphatic amino group made possible the regioselective acylation of the aniline amino group in aryl alkyl diamines under the action of such classical protective agents as CbzCl and FmocCl. The developed method does not require separate steps of protection and deprotection of the more reactive $AlkNH_2$ group, involves the use of minimal amounts of an organic solvent, and therefore meets the concept of green chemistry. The proposed method for protecting a less active amino group in the presence of a more active one can be possibly used in the chemistry of polyamines containing amino groups of various nature as well as in industrial synthesis.

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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.2023.01.004.

References

1 A. S. Nagle, R. N. Salvatore, R. M. Cross, E. A. Kapxhiu, S. Sahab, C. H. Yoon and K. W. Jung, *Tetrahedron Lett.*, 2003, **44**, 5695.
2 P. G. McDougal, J. G. Rico, Y. I. Oh and B. D. Condon, *J. Org. Chem.*, 1986, **51**, 3388.
3 A. Favre-Réguillon, F. Segat-Dioury, L. Nait-Bouda, C. Cosma, J. M. Siaugue, J. Foos and A. Guy, *Synlett*, 2000, 868.
4 F. Alonso, S. G. Davies, A. S. Elend and J. L. Haggitt, *J. Chem. Soc., Perkin Trans. 1*, 1998, 257.
5 S. G. Gouin, J.-F. Gestin, K. Joly, A. Loussouarn, A. Reliquet, J. C. Meslin and D. Deniaud, *Tetrahedron*, 2002, **58**, 1131.
6 N. E. Borisova, M. D. Reshetova, M. V. Kuznetcov and Y. A. Ustynyuk, *Synthesis*, 2007, 1169.
7 J. M. Hah, P. Martásek, L. J. Roman and R. B. Silverman, *J. Med. Chem.*, 2003, **46**, 1661.
8 T. Hashimoto and K. Maruoka, *Org. Biomol. Chem.*, 2008, **6**, 829.
9 A. Sonousi and D. Crich, *Org. Lett.*, 2015, **17**, 4006.
10 D. Bogdal, M. Lukasiewicz and J. Pielichowski, *Synth. Commun.*, 2005, 37.
11 P. Juszczyk, L. Łankiewicz and A. S. Kołodziejczyk, *Lett. Pept. Sci.*, 2002, **9**, 187.
12 J. F. King, R. Rathore, J. Y. L. Lam, Z. R. Guo and D. F. Klassen, *J. Am. Chem. Soc.*, 1992, **114**, 3028.
13 J. F. King, Z. R. Guo and D. F. Klassen, *J. Org. Chem.*, 1994, **59**, 1095.
14 V. Perron, S. Abbott, N. Moreau, D. Lee, C. Penney and B. Zacharie, *Synthesis*, 2009, 283.
15 A. G. Balybin, Yu. M. Panov, L. V. Erkhova, D. A. Lemenovskii and D. P. Krut’ko, *Mendeleev Commun.*, 2019, **29**, 438.

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