A Mild and Efficient Modified Hofmann Rearrangement

Xicai Huang, Mehran Seid, and Jeffrey W. Keillor*

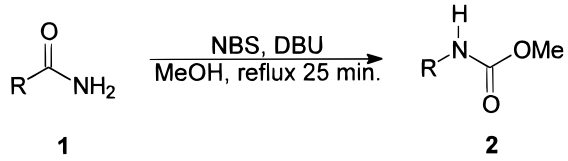
Département de chimie, Université de Montréal, C.P. 6128, Succursale centre-ville, Montréal, PQ, H3C 3J7 Canada

Received May 13, 1997

The classical Hofmann rearrangement is the conversion of a primary carboxamide to a primary amine using aqueous NaOH and Br_2.[1] In order to improve the reaction conditions and yield, many modifications have been made by using oxidative reagents including iodine(III) species,[2] lead tetraacetate,[3] benzyltrimethylammonium tribromide,[4] NBS−$Hg(OAc)_2$,[5] and CH_3OBr.[6] When methanol is used as a solvent, the corresponding methyl carbamate is produced. However, clean conversion of *p*-methoxybenzamide to its corresponding methyl carbamate is impossible through the use of the oxidants mentioned above because they cause further oxidation of the product. Recently, we reported[7] an alternative method for the preparation of *p*-anisidine through the use of NBS in the presence of NaOMe in methanol. This method was shown to be broadly useful for the conversion of carboxamides to their corresponding methyl carbamates. Its principal disadvantage is its use of a strong base (NaOMe); in addition, this method is not capable of effecting the rearrangement of either *p*-(dimethylamino)benzamide or *p*-nitrobenzamide. However, following further modification of the reaction conditions, we are now able to prepare a wide series of methyl carbamates that includes these two compounds. Herein we report a mild and efficient modified Hofmann rearrangement through the use of NBS and DBU in methanol (Scheme 1).

As shown in Table 1, this modification is widely useful for the conversion of alkyl and aryl carboxamides to their corresponding methyl carbamates in excellent yields under extremely mild conditions. The reaction is usually complete in 25 min in boiling methanol, in the presence of NBS. Two equivalents of NBS were generally used to ensure complete conversion. Even *p*-nitrobenzamide undergoes rearrangement, although not quite as rapidly. For the long chain aliphatic amides, a large volume of methanol was used in order to avoid the formation of *N*,*N*′-dialkylurea. For example, for the reaction of $CH_3(CH_2)_{14}CONH_2$ in the presence of 5 mL of methanol on a 0.5 mmol scale, the major product was the urea; however, in the presence of 50 mL of methanol the yield of the desired methyl carbamate was increased to 70%.

Scheme 1



1 **2**

Table 1. Conversion of Primary Amides 1 to Methyl Carbamates 2 with NBS/DBU

$RCONH_2$[a] R =	yield of **2** (%)[b]	obs. mp (°C)[c]	lit. mp (°C)	method	ref
p-$MeOC_6H_4$	95	87−89	88−89	A	8
3,4-$(MeO)_2C_6H_3$	89	80−81	81	A	9
p-MeC_6H_4	84	98−99	99−101	A	10
C_6H_5	95	45−46	47−48.5	A	10
p-ClC_6H_4	94	113−115	115−117	A	10
p-$NO_2C_6H_4$	70	177−178	177.5−178	A[d]	11
$C_6H_5CH_2$	95	64−65	65	A	12
$CH_3(CH_2)_8$	90	<rt		A[e]	13
$CH_3(CH_2)_{14}$	73	61−62	61−62	A[e]	1
2,4-$(MeO)_2C_6H_3$	68	55−56		B	14
p-$(CH_3)_2NC_6H_4$	43	98−100	100−102	B	15

[a] Prepared from the corresponding carboxylic acid or acid chloride. [b] Refers to pure isolated and characterized product. [c] Determined in capillary tubes and uncorrected. [d] Overnight reflux. [e] 50 mL of MeOH for 0.5 mmol of amide.

This modified method is most useful for the conversion of benzamides with strongly electron-donating substituents. With 2,4-dimethoxybenzamide and 4-(dimethylamino)benzamide, 1 equiv of NBS was added at −78 °C to avoid bromination of the benzene ring, and then the mixture was kept at room temperature for 4 h. Good to moderate yields result under these conditions, and the unreacted starting material can easily be recovered and recycled. When 2 equiv of NBS was used, no rearrangement occurred; rather, electrophilic aromatic monobromination of the benzamides was found to be the major reaction. An attempt was made to effect the rearrangement of *p*-hydroxybenzamide, but even at -78 °C in the presence of 1 equiv of NBS, mono-bromination of the benzene ring still occurred more rapidly than the rearrangement, which was not observed.

Recently, Sananyake and co-workers reported[16] that in aqueous potassium hydroxide the active brominating species derived from NBS is $KO_2CCH_2CH_2CONKBr$, which was found to decompose at 20 °C. In our previously reported use of NBS in boiling methanol in the presence of NaOMe, we suggested[7] that the brominating species is the analogous $MeO_2CCH_2CH_2CONNaBr$, which is able to effect the desired rearrangement prior to its decomposition. In order to determine the brominating species in the present study, the byproducts of the reaction of benzamide with 2 equiv of NBS were isolated

(1) Wallis, E .S.; Lane, J. F. *Org. React.* **1946**, *3*, 267−306.
(2) Moriarty, R. M.; Chany, C. J., II; Vaid, R. K.; Prakash, O.; Tuladhar, S. M. *J. Org. Chem.* **1993**, *58*, 2478−2482.
(3) Baumgarten, H. E.; Smith, H. L.; Staklis, A. *J. Org. Chem.* **1975**, *40*, 3554−3561.
(4) Kajigaeshi, S.; Asano, K.; Fujisaki, S.; Kakinami, T.; Okamoto, T. *Chem. Lett.* **1989**, 463−464.
(5) Jew, S.-S.; Park, H. G.; Park, H.-J.; Park, M.-S.; Cho, Y.-S. *Tetrahedron Lett.* **1990**, *31*, 1559−1562.
(6) Radlick, P.; Brown, L. R. *Synthesis* **1974**, 290−292.
(7) Huang, X; Keillor, J. W. *Tetrahedron Lett.* **1997**, *38*, 313−316.
(8) Esch, P. M.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1992**, *48*, 3445−3462.
(9) Experimental data: ^{1}H NMR (300 MHz, $CDCl_3$) 3.75 (s, 3H), 3.85 (s, 3H), 3.89 (s, 3H), 6.64 (bs, 1H), 6.74−6.78 (m, 2H), 7.10−7.22 (b, 1H). Literature melting point: Brunner, O.; Wöhrl, R. *Monatsh.* **1933**, *63*, 374−384.
(10) Fujisaki, S.; Tomiyasu, K.; Nishida, A.; Kajigaeshi, S. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1401−1403.
(11) Hegarty, A. F.; Frost, L. N. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1719−1728.
(12) de la Saulnière, P. C. *Ann. Chim.* **1942**, *17*, 353−370.
(13) Experimental data: HRMS ($M^+ + 1$) = 202.17990
(14) Experimental data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.76 (s, 3H), 3.80 (s, 3H), 3.85 (s, 3H), 6.45−6.52 (m, 2H), 6.98 (bs, 1H), 7.82−7.89 (b, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.831, 148.993, 143.520, 121.005, 119.120, 103.768, 98.656, 55.604, 55.496, 52.131. Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.22; N, 6.63. Found: C, 56.89; H, 6.36; N, 6.60.
(15) Laidlaw, R. K.; Miura, Y.; Panetta, C. A. *Acta. Crystallogr.* **1988**, *C44*, 2009−2013.
(16) Senanayake, C. H.; Fredenburgh, L. E.; Reamer, R. A.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *J. Am. Chem. Soc.* **1994**, *116*, 7947−7948.

S0022-3263(97)00855-4 CCC: $14.00

by flash column chromatography and identified by proton NMR. The major byproducts were found to be succinimide (1.3 equiv) and $MeO_2CCH_2CH_2CONH_2$ (0.4 equiv), suggesting that in the absence of methoxide the active brominating species may be simply NBS. This species is probably also unstable in boiling methanol, but when excess NBS is added in two portions, the active brominating species is apparently sufficiently long-lived to promote rearrangement.

Kajigaeshi and co-workers have reported[17] the use of DBU as a base for the Hofmann rearrangement (in their case, with tetrabutylammonium tribromide), and it appears as though DBU is particularly well suited to effect the rearrangement. For example, in the absence of DBU, we have found that 4-(dimethylamino)benzamide reacts with NBS to undergo only mono-bromination at room temperature, and no rearrangement occurs. Furthermore, when an attempt was made to use NEt_3 in place of DBU, no rearrangement was observed for benzamide even at higher temperatures. Apparently NEt_3, while only slightly less basic than DBU, is not a strong enough base to promote the rearrangement.

Our conditions for the modified Hofmann rearrangement are among the mildest available. Surprisingly, our conditions are also widely useful, and the series of amides that we have easily and efficiently transformed into methyl carbamates is one of the broadest reported to date.[18] This reaction should therefore be very useful for the practical transformation of primary amides to their corresponding primary amines for an extremely wide range of both aromatic and aliphatic compounds.

(17) Fujisaki, S.; Tomiyasu, K.; Nishida, A.; Kajigaeshi, S. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1401−1403.

(18) Furthermore, when the reaction of benzamide with NBS in the presence of DBU is carried out in benzyl alcohol, the corresponding benzyl carbamate is isolated in 76% yield. When the reaction is carried out in water, aniline is obtained directly in 50% yield.

General Representative Experimental Procedures

Method A. *p*-Methoxybenzamide (76 mg, 0.5 mmol), NBS (90 mg, 0.5 mmol), and DBU (230 μL) in methanol (5 mL) were heated at reflux for 15 min, at which point more NBS (90 mg, 0.5 mmol) was added. The reaction was allowed to continue for another 10 min. Methanol was then removed by rotary evaporation, and the residue was dissolved in 50 mL of EtOAc. The EtOAc solution was washed with 5% HCl and saturated $NaHCO_3$ and was then dried over $MgSO_4$. The product, methyl (*p*-methoxyphenyl)carbamate, was purified by flash column chromatography (silica gel, eluant 5% EtOAc in CH_2Cl_2) to give a white solid (86 mg, 95%), which was further purified by recrystallization from hexane, mp 87−89 °C (lit.[8] mp 88−89 °C).

Method B. 2,4-Dimethoxybenzamide (91 mg, 0.5 mmol) and DBU (230 μL) in methanol (5 mL) and CH_2Cl_2 (5 mL) were cooled to −78 °C, followed by the addition of NBS (90 mg, 0.5 mmol). The resulting mixture was stirred at −78 °C for 30 min until all of the NBS was dissolved and then allowed to warm up slowly to room temperature. Stirring was continued at room temperature for another 4 h. Methanol was removed by rotary evaporation, and the residue was purified directly by flash column chromatography (silica gel, eluant 5% EtOAc in CH_2Cl_2) to give the product, methyl (2,4-dimethoxyphenyl)carbamate,[14] isolated as an oil (69 mg, 68%) which was further purified through recrystallization from hexane, mp 55−56 °C.

Although the results reported in Table 1 are based on the mmol-scale procedures described above, we have found that gram-scale reactions also afforded the methyl carbamates in similar yields.

Acknowledgment. The authors gratefully acknowledge the financial support of the University of Montréal, the Natural Sciences and Engineering Research Council (NSERC) of Canada, and the Fonds pour la formation de chercheurs et l'aide à la recherche (FCAR) of Québec.

JO9708553