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Syntheses

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# Working with Hazardous Chemicals

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*September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

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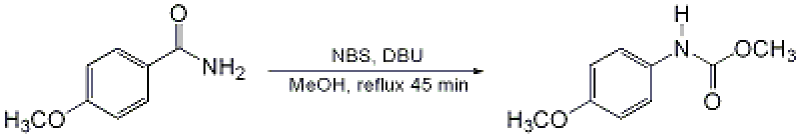
# METHYL CARBAMATE FORMATION VIA MODIFIED HOFMANN REARRANGEMENT REACTIONS: METHYL N-(p-METHOXYPHENYL)CARBAMATE

## [ Carbamic acid, (4-methoxyphenyl)-, methyl ester ]



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Checked by Scott Ceglia and Edward J. J. Grabowski.

## 1. Procedure

To a 1-L, round-bottomed flask equipped with a stirring bar are added p-methoxybenzamide (10 g, 66 mmol), N-bromosuccinimide (NBS) (11.9 g, 66 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (22 mL, 150 mmol) and methanol (300 mL) (Note 1). The solution is heated at reflux for 15 min (Note 2), at which point an additional aliquot of NBS (11.9 g, 66 mmol) is added slowly. The reaction is allowed to continue for another 30 min (Note 3). Methanol is removed by rotary evaporation and the residue is dissolved in 500 mL of ethyl acetate (EtOAc). The EtOAc solution is washed with 6 N hydrochloric acid (HCl) (2 × 100 mL), 1 N sodium hydroxide (NaOH) (2 × 100 mL) and saturated sodium chloride (NaCl), and then dried over magnesium sulfate ($MgSO_4$). The solvent is removed by rotary evaporation and the product, methyl N-(p-methoxyphenyl)carbamate, is purified by flash column chromatography [ 50 g of silica gel, EtOAc / hexane (1:1)] to give a pale yellow solid (11.1 g, 93%), which is further purified by recrystallization from 500 mL of hexane (Note 4). Another 1.4 g of product (total 8.8 g, 73%) is obtained from the mother liquor by recrystallization from 100 mL of hexane .

## 2. Notes

1. p-Methoxybenzamide, NBS and DBU were purchased from the Aldrich Chemical Company, Inc.
2. The reaction mixture is heated using an oil bath.
3. Reaction progress can be followed by thin layer chromatography using EM Science silica gel 60 F254 aluminum-backed plates, eluted with EtOAc/hexane (1:1) and visualized using a 254 nm UV lamp.
4. Methyl N-(p-methoxyphenyl)carbamate prepared by this procedure was characterized as follows: mp (uncorr.) 88.5-89.5°C (lit.[2] mp 88-89°C); $^1H$ NMR (500 MHz, $CDCl_3$) δ: 3.77 (s, 3 H), 3.78 (s, 3 H), 6.50 (bs, 1 H), 6.90 (m, 2 H), 7.26 (m, 2 H) ; $^{13}C$ NMR (100 MHz, $CDCl_3$) δ: 52.1, 55.3, 114.1, 120.6, 130.9, 154.5, 155.8 ; FTIR spectrum ($CHCl_3$) $cm^{-1}$: 3437, 3080, 2963, 1734, 1600, 1511, 1464, 1298, 1226, 1181, 1076, 1035 ; Calcd for $C_9H_{11}NO_3$: C, 59.7; H, 6.1; N, 7.7. Found: C, 59.6; H, 6.3; N, 7.7.

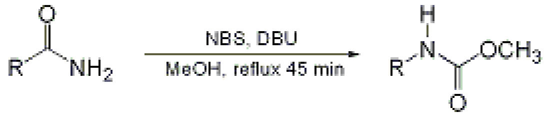
## Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

## 3. Discussion

This method offers a rapid, efficient and particularly mild preparation of methyl carbamates, and has been used with success with a variety of primary amides[3] (see Table). These carbamates are easily hydrolyzed to free amines, making this method particularly useful for making $^{15}N$-labeled anilines containing electron-donating substituents, such as p-anisidine , 2,4-dimethoxyaniline and 4-dimethylaminoaniline . Although other methods are available for the preparation of methyl carbamates, including the use of NaOH/$Br_2$,[4] iodine(III) species,[5] lead tetraacetate ,[6] and NBS-$Hg(OAc)_2$,[7] none of these methods are mild enough to permit the clean conversion of p-methoxybenzamide , since they cause further oxidation of the product. Currently, the best alternative method is the use of NBS/NaOMe reported earlier by this laboratory.[8]

TABLE
CONVERSION OF AMIDES TO METHYL CARBAMATES WITH NBS/DBU



| R[a] | Yield,[b] (%) | Obs. mp,[c] (°C) | Lit. mp, (°C) |
|---|---|---|---|
| 3,4-$(MeO)_2C_6H_3$- | 89 | 80-81 | 81 [d] |
| p-$MeC_6H_4$- | 84 | 98-99 | 99-101 [e] |
| $C_6H_5$- | 95 | 45-46 | 47-48.5 [e] |
| p-$ClC_6H_4$- | 94 | 113-115 | 115-117 [e] |
| p-$NO_2C_6H_4$- | 70 [f] | 177-178 | 177.5-178 [g] |
| $C_6H_5CH_2$- | 95 | 64-65 | 65 [h] |
| $CH_3(CH_2)_8$- | 90 | < r.t. | – |
| $CH_3(CH_2)_{14}$- | 73 | 61-62 | 61-62 [i] |

[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] Brunner, O.; Wöhrl, R. *Monatsh.* **1933**, *63*, 374-384.
[e] Fujisaki, S.; Tomiyasu, K.; Nishida, A.; Kajigaeshi, S. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1401-1403.
[f] Overnight reflux.
[g] Hegarty, A. F.; Frost, L. N. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1719-1728.
[h] Chabrier de la Saulnière, P. *Ann. Chim.* **1942**, *17*, 353-370.
[i] Reference 3.

## References and Notes

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## Appendix
## Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Methyl N-(p-methoxyphenyl)carbamate:
Carbamic acid, (4-methoxyphenyl)-, methyl ester (9); (14803-72-6)

p-Methoxybenzamide:
Benzamide, 4-methoxy- (9); (3424-93-9)

N-Bromosuccinimide:
Succinimide, N-bromo- (8);
2,5-Pyrrolidinedione, 1-bromo- (9); (128-08-5)

1,8-Diazabicyclo[5.4.0]undec-7-ene: DBU:
Pyrimido[1,2-a]azepine, 2,3,4,6,7,8,9,10-octahydro- (8,9); (6674-22-2)