

An efficient modification of the Hofmann rearrangement: synthesis of methyl carbamates

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Abstract—A series of methyl carbamates was synthesized using NaOCl as an oxidant in the presence of KF/Al₂O₃/MeOH at reflux in excellent yields.

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1. Introduction

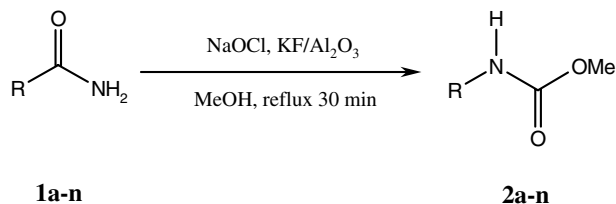
The discovery of the Hofmann rearrangement goes back a long way in organic synthesis.¹ This rearrangement reaction is particularly useful for the synthesis of amines from carboxamides.² The classical method for this transformation involves the use of an alkaline solution of bromine, however, it is unsatisfactory and unreliable.³ Numerous modifications of this rearrangement have been reported using a variety of oxidants and bases, such as iodine(III) reagents⁴ [PhI(OCOCF₃)₂, PhI–HCO₂H, PhI(OTs)OH and PhI(OAc)₂]; lead tetraacetate,⁵ benzyltrimethylammonium tribromide,^{3b} (NBS)–Hg(OAc)₂,⁶ NBS–NaOMe,⁷ NBS–DBU⁸ and MeOBr.⁹

The use of solid-supported reagents has become ubiquitous due to their unique properties, such as enhanced reactivity, selectivity, mild conditions and avoidance of cumbersome aqueous work-ups and a decrease in solvent waste.¹⁰ For example, KF/Al₂O₃ is known to be a useful and interesting solid-supported strong base, which has led to it replacing organic bases in a variety of reactions.¹¹ On the other hand, sodium hypochlorite is an inexpensive, convenient and safe alternative to the currently employed oxidants.¹² It has been used extensively in various organic transformations¹³ such as dehydration of primary/substituted acetamides to nitriles,^{13b} the preparation of polyvinylamine from polyacrylamide^{13c} and the Hofmann degradation of an acryl-

amide copolymer.^{13d} Due to the high selectivity and the ease of product isolation from the solid-supported base, we were compelled to investigate KF/Al₂O₃ along with NaOCl as an efficient reagent system for the Hofmann rearrangement. To the best of our knowledge, this is the first report in which KF/Al₂O₃ is used as a base with NaOCl in the presence of methanol for the synthesis of methyl carbamates.

We report here a simple and economic procedure for the direct synthesis of methyl carbamates from carboxamides, in which NaOCl is used as an oxidant with a catalytic amount of KF/Al₂O₃ (40% KF in Al₂O₃) in MeOH at reflux (Scheme 1).

In Table 1, a variety of aliphatic as well as aromatic amides are smoothly converted to their corresponding methyl carbamates in good to excellent yields. During the reaction, other functional groups such as alkyl, methoxy, chloro, remained intact. When sulfur- or nitrogen-containing heterocycles (entries **1l–1n**) were used as substrates, the reaction occurred smoothly giving excellent yields of the corresponding methyl carbamates. No chlorinated product was observed when an

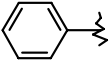
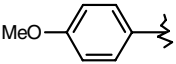
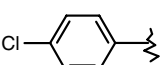
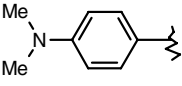
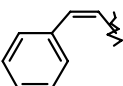
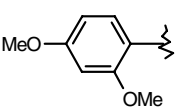
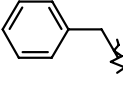
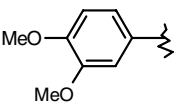
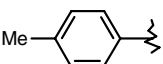
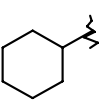
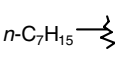





Scheme 1. Synthesis of methyl carbamates.

Keywords: Hofmann rearrangement; Methyl carbamate; KF/Al₂O₃; NaOCl.

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Table 1. Synthesis of methyl carbamates from primary amides

RCONH ₂	R	RNHCO ₂ Me	Yield (%)	Mp (°C)	
				Obsd	Lit.
1a		2a	95	46–47	45–46 ⁸
1b		2b	94	88	88–89 ¹⁴
1c		2c	90	113–116	115–117 ¹⁵
1d		2d	73	99–100	100–102 ¹⁶
1e		2e	85	—	Oil
1f		2f	80	57	55–56 ⁸
1g		2g	79	66–67	64–65 ⁸
1h		2h	88	81	80–81 ⁸
1i		2i	87	97–98	99–101 ¹⁵
1j		2j	84	73–75	72–75 ⁹
1k	$n\text{-C}_7\text{H}_{15}$ 	2k	72	—	Liquid
1l		2l	91	88–90	—
1m		2m	90	119–121	117–118 ^{4b}
1n		2n	83	128–129	128–129 ^{4b}

amide containing a double bond was used as a substrate (entry **1e**).

KF/Al₂O₃ derives its basicity from the formation of KOH in the initial preparation of the solid-supported material by the reaction of KF with alumina supports.¹¹ Under the highly basic reaction conditions, OCl⁻ is the predominant form of chlorine, which reacts with the

amide to form *N*-chloroamide which undergoes rearrangement to the isocyanate. In the presence of methanol the isocyanate forms a methyl carbamate.

This modified Hofmann rearrangement is simple and inexpensive and is applicable to a variety of aliphatic as well as aromatic amides for the synthesis of methyl carbamates.

2. Experimental

2.1. Typical experimental procedure for the synthesis of methyl carbamate

To a solution of benzamide (1 mmol) in methanol (7 ml), KF/Al₂O₃ (2 g, 40% by weight) and NaOCl (3 ml of a 4% aqueous solution) were added and the mixture was refluxed for 30 min. After cooling the reaction mixture to room temperature, the solid base was filtered. Methanol was then removed by rotary evaporation and the residue was dissolved in EtOAc (20 ml). The EtOAc layer was washed with water (10 ml × 3), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a crude product which was purified by crystallization using petroleum ether.

2.2. Methyl *N*-(2-thiophene)carbamate (2I)

White solid; mp 88–90 °C; ¹H NMR (CDCl₃, 300 MHz): δ 3.80 (s, 3H), 6.60 (d, 1H, *J* = 2.46 Hz), 6.80–6.88 (m, 2H), 7.20 (br s, 1H); ¹³C NMR (CDCl₃, 75 MHz): δ 53.82, 113.29, 118.47, 125.53, 140.67, 154.87; FTIR (KBr): 3257, 2960, 1696, 1576, 1349, 1289, 1249, 1071 cm⁻¹; HRMS calcd for C₆H₇NO₂S (M⁺) 157.1923, found 157.4601.

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