

Radical Mediated Oxidations in Organic Chemistry. 3. An Efficient and Versatile Transformation of Aldehydes into Amides [‡].

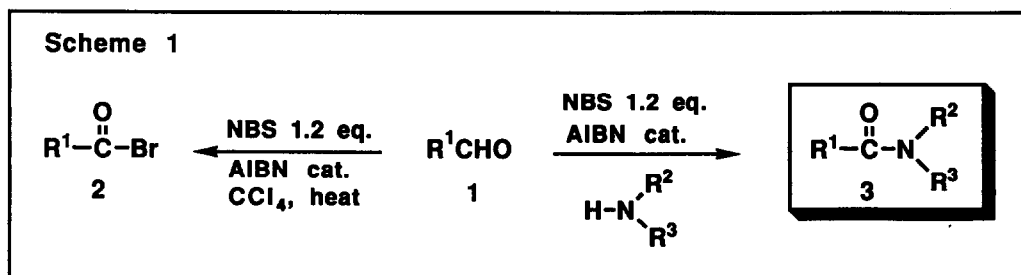
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Abstract: The neutral, radical-mediated, oxidation of aldehydes into acid bromides and amides is reported.

We have reported previously the efficient, radical-promoted, oxidation of benzylic trimethylsilyl ethers to the corresponding carbonyl compounds and the oxidation of primary aliphatic trimethylsilyl ethers to simple esters using an equimolar amount of *N*-Bromosuccinimide (NBS) in the presence of a catalytic quantity of AIBN as a radical initiator ¹. With the view of increasing the scope of this neutral oxidation reaction, we successfully investigated the transformation of aldehydes into esters ².

We now report the smooth formation and isolation of some acid bromides from aldehydes ³ as well as the direct transformation of these aldehydes into amides ⁴ (Scheme 1). These results considerably broaden the scope of this neutral oxidation method .

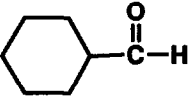
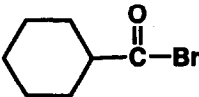


When stoichiometric quantities of an aldehyde 1 and NBS were heated in CCl_4 , in the presence of a catalytic amount of AIBN, a rapid reaction was observed and succinimide precipitated readily. Filtration gave essentially pure acid bromide 2 which could, in some cases, be isolated by distillation ⁵ (Table 1). In general, however, the crude acid bromides obtained were of sufficient purity to be used as such in the subsequent steps.

As can be seen from Table 1, aldehydes of wide structural variety can be employed with equal success. In all cases examined so far, the reaction was

complete within 10 to 15 minutes; the only exception being the transformation of benzaldehyde into benzoyl bromide which required 30 minutes. Reactions of the acid bromides with various nucleophiles were then studied. However, because of the thermal and moisture sensitivity of these acid halides, it was easier to prepared them *in situ* and used them immediately, without further purification.

Table 1. Transformation of aldehydes into acid bromides

Entry	Substrate	Product	Yields (a)
1	$\text{C}_6\text{H}_{13}-\overset{\text{O}}{\parallel}{\text{C}}-\text{H}$	$\text{C}_6\text{H}_{13}-\overset{\text{O}}{\parallel}{\text{C}}-\text{Br}$	78%
2			83% (77%)
3	$t\text{-Bu}-\overset{\text{O}}{\parallel}{\text{C}}-\text{H}$	$t\text{-Bu}-\overset{\text{O}}{\parallel}{\text{C}}-\text{Br}$	85%
4	$\text{Ph}-\overset{\text{O}}{\parallel}{\text{C}}-\text{H}$	$\text{Ph}-\overset{\text{O}}{\parallel}{\text{C}}-\text{Br}$	87% (78%)

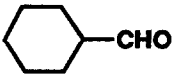
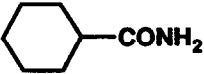
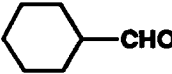
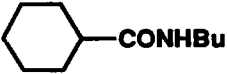
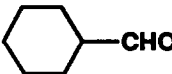
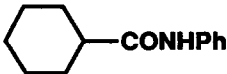
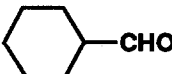
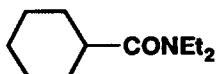
(a) = yields were determined by NMR using an internal standard; yields into brackets are for isolated, purified material.

Therefore, the reaction mixture, containing the precipitated succinimide and the crude acid bromides, was cooled to 0°C and **directly** treated with a slight excess of amine. **High and reproducible yields of amides were obtained following this procedure** (Table 2).

The reaction is successful with a whole variety of aldehydes and amines, including ammonia and aniline, and offers a particularly simple and attractive route for the direct transformation of aldehydes into amides. It is worth noting that if only few efficient methods exist to transform aldehydes into esters, even fewer methods are available to convert aldehydes directly into amides ⁶.

This two step, one-flask operation therefore nicely complements our previously reported oxidation method ^{1, 2}. Further investigations into the scope and application of this smooth and versatile oxidation procedure are being actively pursued.

Table 2. Preparation of amides from aldehydes.

Entry	Substrate	Amine	Product	Yields
1		NH ₃		76%
2		BuNH ₂		80%
3		PhNH ₂		94%
4		Et ₂ NH		65%
5	Ph-CHO	BuNH ₂	Ph-CONHBu	80%
6	Ph-CHO	Et ₂ NH	Ph-CONEt ₂	78%
7	C ₆ H ₁₃ -CHO	BuNH ₂	C ₆ H ₁₃ -CONHBu	78%
8	C ₆ H ₁₃ -CHO	Et ₂ NH	C ₆ H ₁₃ -CONEt ₂	75%
9	<i>t</i> -Bu-CHO	BuNH ₂	<i>t</i> -Bu-CONHBu	70%
10	<i>t</i> -Bu-CHO	Et ₂ NH	<i>t</i> -Bu-CONEt ₂	95%

Acknowledgement

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Typical experimental procedure.

Preparation of *N*-Butyl-cyclohexyl carboxamide.

To a solution of cyclohexylcarboxaldehyde (2 g, 17.85 mmol) in 50 mL of dry CCl₄, were added, sequentially, AIBN (50 mg, 0.3 mmol) and NBS (4.13 g, 23.21 mmol). The

flask was then placed in an oil-bath preheated at 95°C and the heterogeneous mixture stirred for 12 minutes ⁶. The crude reaction mixture was cooled to 0°C (ice-water bath) and *n*-butylamine (3 g, 41.1 mmol) was added dropwise. The ice-bath was removed and the suspension was stirred at room temperature for 10 minutes. The solid material was removed by filtration and washed with 20 mL of CCl₄. The filtrate was extracted with water (2x30 mL), dried over MgSO₄ and concentrated *in vacuo* to give a viscous oil. This crude product was purified by column chromatography on silica gel (ethyl acetate - petroleum ether 1:4) to give 2.6 g (80% yield) of *N*-butyl-cyclohexyl carboxamide as a white crystalline material. mp: 59-62°, IR (KBr, cm⁻¹) 3290, 1635, 1550; ¹H NMR (220MHz, CDCl₃) δ: 0.90 (t, 3H, J=7.5Hz), 1.20-1.90 (m, 14H), 2.16 (m, 1H), 3.20 (q, 2H, J=7.5Hz), 6.76 (s, 1H); ¹³C NMR (60 MHz, CDCl₃) δ: 176.06, 45.32, 38.82, 31.57, 29.53, 25.58, 19.87, 13.56; MS (EI) 183, (CI) 184.

‡ Dedicated to Professor W. D. Ollis, at the occasion of his 65th Birthday.

References

- 1 Markó, I. E.; Mekhalfia, A.; Ollis, W. D. *Synlett.*, **1990**, 345.
- 2 Markó, I. E.; Mekhalfia, A.; Ollis, W. D. *Synlett.*, **1990**, 347.
- 3 A photochemical transformation of aldehydes into acid bromides, in modest yields, has been previously reported: Cheung, Y.-F. *Tetrahedron Lett.*, **1979**, 3809.
- 4 Only a few examples of direct preparation of amides from aldehydes were reported: a. Yamaguchi, M.; Adachi, T. *Nippon Kagaku Zasshi*, **1958**, *79*, 487. b. Gilman, N. W. *J. Chem. Soc., Chem. Commun.*, **1971**, 733. c. Nakagawa, K.; Onoue, H.; Minami, K. *J. Chem. Soc., Chem. Commun.*, **1966**, 17.
- 5 In some cases, attempted distillation resulted in considerable loss or total decomposition of the acid bromide.
- 6 At this stage, purification of the acid bromide was performed as follows: The crude reaction mixture was cooled to 0°C and the precipitated succinimide removed by filtration. The filtrate was concentrated *in vacuo* to give an orange oil which was carefully distilled to yield 2.62 g (77%) of pure acid bromide as a nearly colourless oil. All these operations were performed under argon and with complete exclusion of moisture.

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