

FACILE ONE-POT CONVERSION OF ALDEHYDES INTO AMIDES

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A facile one-pot synthesis of amides from aldehydes has been developed. This tandem process involves the formation of a nitrile intermediate obtained from the reaction of an aldehyde with hydroxylamine hydrochloride in dimethylsulfoxide at 100°C and the subsequent treatment of the nitrile with basic hydrogen peroxide. The resulting amide products were produced in good yields (67–95%) and purity (>95%).

Keywords: Aldehyde; amide; hydrogen peroxide; nitrile; tandem reaction

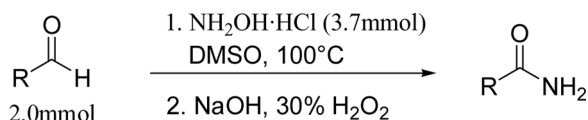
Nitriles are versatile synthetic intermediates because they can be transformed into a variety of other functional groups.^[1,2] One such transformation is the selective hydrolysis of nitriles into amides.^[3] In part because of their unique electronic and structural properties,^[4] amides are particularly important functional groups and are found in a number of natural products, polymers, and pharmaceuticals. Thus, methods for preparing amides are highly desirable.

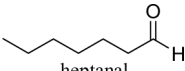
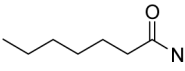
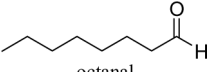
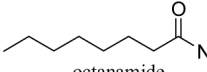
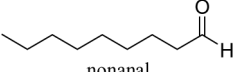
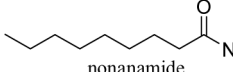
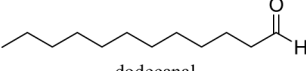
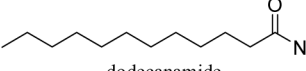
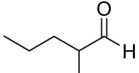
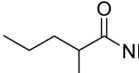
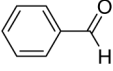
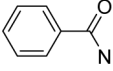
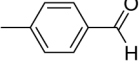
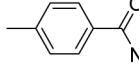
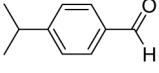
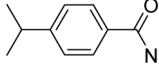
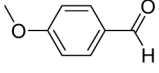
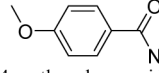
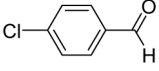
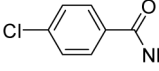
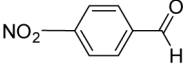
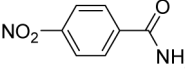
Recently,^[5] we described a convenient one-pot synthesis of nitriles from aldehydes using hydroxylamine hydrochloride in dimethylsulfoxide (DMSO) at 100°C. We have now extended this synthetic methodology to the one-pot conversion of aldehydes into amides and report our findings herein.

The experimental procedure for the one-pot conversion of aldehydes to amides is simple and straightforward and affords amides in good isolated yields (Table 1). As an illustrative example, octanal (2.0 mmol) was added to a solution of hydroxylamine hydrochloride (3.8 mmol) in DMSO (4 mL), and the resulting reaction solution was stirred and heated for 30 min in a sand bath maintained at 100°C. Upon removal of the sand bath, but while still hot, aqueous sodium hydroxide (1 mL of 5.68 M, 5.68 mmol) was slowly added to the reaction mixture over a 1-min period with stirring, followed by the slow and careful addition of 30% hydrogen peroxide (2.5 mL) over a 5-min period. After stirring for 1 min, the reaction mixture was extracted with ether (4 × 20 mL), and the combined ether layers were washed with water (4 × 20 mL) and dried (MgSO₄). Removal of the ether

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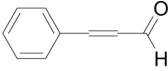
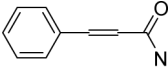
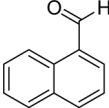
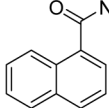
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Table 1. Facile one-pot synthesis of amides from aldehydes

Entry	Aldehyde	Amide	Yield (%) ^a	Time ^a
1	 heptanal	 heptanamide	84	30
2	 octanal	 octanamide	94	30
3	 nonanal	 nonanamide	95	30
4	 dodecanal	 dodecanamide	88	30
5	 2-methylpentanal	 2-methylpentanamide	87	60
6	 benzaldehyde	 benzamide	70	60
7	 4-methylbenzaldehyde	 4-methylbenzamide	90	60
8	 4-isopropylbenzaldehyde	 4-isopropylbenzamide	95	60
9	 4-methoxybenzaldehyde	 4-methoxybenzamide	90	30
10	 4-chlorobenzaldehyde	 4-chlorobenzamide	86	60
11	 4-nitrobenzaldehyde	 4-nitrobenzamide	67	30

(Continued)

Table 1. Continued

Entry	Aldehyde	Amide	Yield (%) ^a	Time ^b
12	 <i>trans</i> -3-phenyl-2-propenal	 <i>trans</i> -3-phenyl-2-propenamide	84	30
13	 1-naphthaldehyde	 1-naphthamide	70	60

^aIsolated yields.^bTime for complete conversion to amide.

solvent by rotary evaporation and high vacuum gave octanamide as a white solid (0.231 g, 80% yield). The ¹H and ¹³C NMR spectra and the mass spectra of the isolated octanamide were identical to literature spectra.^[6]

Although no mechanistic studies were performed, it seems reasonable that this tandem conversion of an aldehyde to an amide involves two steps. First, the formation of an aldoxime followed by its dehydration gives a nitrile, and second, the nitrile is selectively hydrolyzed to an amide by the basic hydrogen peroxide, as fully described by Wiberg.^[7]

As seen in Table 1, the reaction is general for the preparation of both aliphatic and aromatic amides. The amides prepared in this study were confirmed by comparison of ¹H and ¹³C NMR spectra and mass spectra with authentic samples. Furthermore, the ¹H and ¹³C NMR spectra of the amide products indicated that the product purities were greater than 95%.

In conclusion, we have demonstrated that aldehydes can be readily converted into amides by heating (100°C) the aldehydes in DMSO containing hydroxylamine hydrochloride, followed by selective hydrolysis of the subsequent nitrile with basic hydrogen peroxide. This one-pot, tandem process does not involve expensive or hazardous materials and should offer an attractive alternative to recently described procedures for converting aldehydes into amides, including the TerpyRu(PPh₃)Cl₂-catalyzed rearrangement of aldoximes to amides,^[8] the metal-free oxidative amination of aromatic aldehydes with *tert*-butyl hydroperoxide,^[9] the treatment of aldehydes with iodine in aqueous ammonia followed by hydrogen peroxide,^[10,11] the rhodium-catalyzed oxidative amination of aldehydes with *N*-methylmorpholine *N*-oxide,^[12] and the treatment of aldehydes with hydroxylamine hydrochloride/wet alumina/methanesulfonyl chloride.^[13]

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