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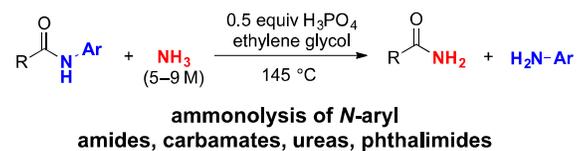


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Table of Contents Entry:

Anilides undergo phosphoric acid-promoted ammonolysis to primary amides in a diol solvent, such as ethylene glycol.

Ammonolysis of Anilides Promoted by Ethylene Glycol and Phosphoric Acid

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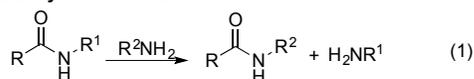
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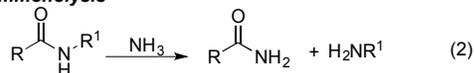
Ethylene glycol (EG) and phosphoric acid have been found to promote the ammonolysis of a variety of diverse anilides as well as *N*-aryl carbamate, phthalimide, and urea substrates in the absence of transition metals or other Lewis acid promoters.

The prominence of carboxamides in synthetic and naturally occurring molecules and polymers can be attributed, at least in part, to the robust nature of the amide functional group. Aminolysis and transamidation reactions [eqn (1)] represent an interesting class of approximately thermoneutral exchange reactions that could have utility in dynamic covalent chemistry or synthetic applications. In 2003, we reported one of the first catalytic methods capable of equilibrating amines and secondary carboxamides.^{1,2} In subsequent years, we³ and others⁴ expanded upon these results to identify new classes of catalysts, improve catalytic activity, and develop synthetically useful methods on the basis of this reactivity. Despite these advances, ammonia has not been shown to serve as an effective reaction partner. The ammonolysis of amides [eqn (2)] would be useful for the conversion secondary or tertiary amides to primary amides or the deprotection of acylated primary or secondary amines. Such methods also provide the basis for the recycling of polyamides, such as nylon and Kevlar.⁵ Here, we report a protocol for the ammonolysis of anilides that is strongly promoted by phosphoric acid in ethylene glycol as a solvent.

Aminolysis/Transamidation



Ammonolysis



Early in this study, we identified two precedents for the direct ammonolysis of amides: (1) the depolymerization of nylon, which typically features Lewis acidic metal salts or heterogeneous catalysts at high temperatures (<250 °C)⁵ and (2) a 1926 PhD thesis describing the ammonolysis of acetanilide

with 10 atm NH₃ and 1.3 equiv NH₄Cl at 275 °C.⁶ In order to pursue more appealing reaction conditions, we selected 2-phenylacetanilide as a substrate. Preliminary studies revealed that our previously reported metal-catalyzed transamidation protocols were not effective with ammonia as the substrate (see below). An alternative strategy, however, was suggested from studies of the ammonolysis of esters, in which water and diols were found to promote the reaction.⁷ The reactivity of 2-phenylacetanilide with ammonia (7 atm) was tested in the presence of a number of different solvents, including water, glycerol, diols, and simple alcohols (Fig. 1). Yields of both products were analysed by gas chromatography. The reaction in water

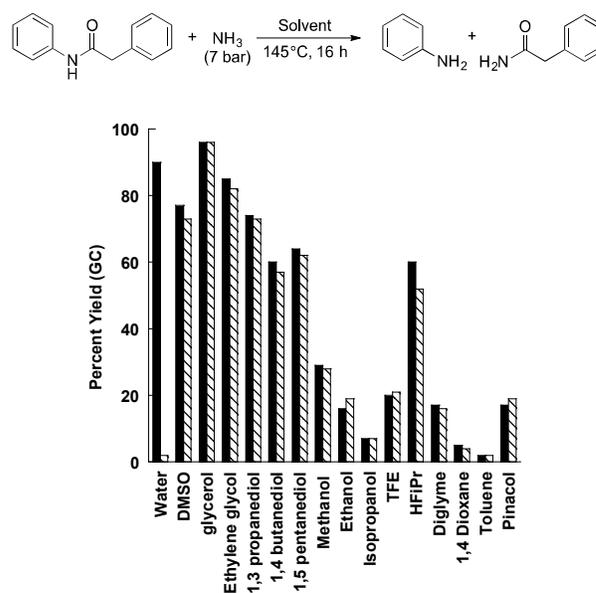


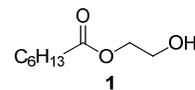
Fig. 1 Yield of aniline (black bars) and 2-phenylacetamide (striped bars) obtained from the ammonolysis of 2-phenylacetanilide (0.5 mmol) in various solvents (5 mL). TFE = trifluoroethanol, HFiPr = 1,1,1,3,3,3 hexafluoro-2-propanol.

afforded good yields of aniline, but only a few percent of phenylacetamide was obtained. Phenylacetic acid was generated as the other major product (~50%). In contrast, good yields of both aniline and 2-phenylacetamide were obtained in glycerol and ethylene glycol. Various other α,ω -diols showed good results, but led to lower yields than with glycerol or ethylene glycol (EG). Hexafluoroisopropanol (HFiPr) was the only mono-alcohol solvent that led to good reactivity, presumably reflecting its ability to promote the reaction via hydrogen bond donation., DMSO was uniquely effective among aprotic solvents, which suggests that solvent polarity could play a role in this reactivity. Poor reactivity was observed in toluene, simple alcohols or ethers. Overall, glycerol led to the best results; however, high viscosity makes glycerol inconvenient, and subsequent ammonolysis reactions were therefore carried out in EG.

The reactivity of heptanilide was then tested, but only 51% yields of aniline and heptanamide were obtained when the ammonolysis was carried out in EG under the conditions of Fig. 1. A variety of Lewis acids (20 mol %) were tested as possible catalysts for the ammonolysis of heptanilide in EG (Fig. 2A). In these reactions, a 5 M solution of NH_3 in EG was used to enhance the operational simplicity of the

method relative to adding NH_3 at high pressure. Numerous reactions containing Lewis acids performed significantly better than the reaction without a Lewis acid. The combination of NH_3 and EG with Lewis acids could generate ammonium salts that serve as Brønsted acid catalysts.⁸ To test this possibility, we evaluated a number of different ammonium salts and other Brønsted acids. Phosphoric acid and mono- and dibasic phosphoric acid salts were especially effective in promoting the desired reactivity (Fig. 2B).

The low cost and ease of working with H_3PO_4 prompted us to continue with this catalyst/promoter. Lower ammonia concentrations (1-3 M) were tested in the H_3PO_4 -promoted ammonolysis of heptanilide, but the yield of heptanamide was lower than the yield of aniline under these conditions. 2-Hydroxyethylheptanoate (**1**), corresponding to the product of esterification of heptanilide with ethylene glycol, was identified as the major by-product (See Figure S3†). Consequently, the $[\text{NH}_3]$ was maintained between 5–9 M in subsequent studies.



The ethylene glycol/phosphoric acid ammonolysis conditions were tested with a number of other heptanamide

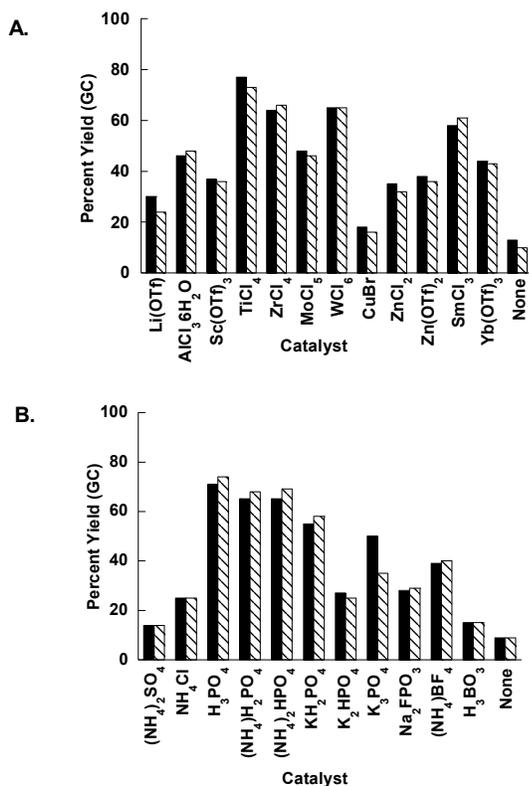
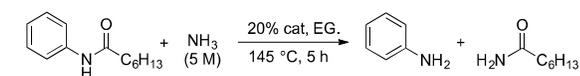
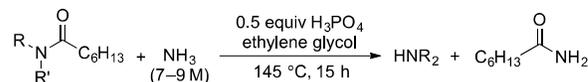


Fig. 2 Effect of Lewis (A) and Brønsted (B) acids on the ammonolysis of heptanilide (2 mmol) in ethylene glycol (5 ml) with dissolved ammonia (5 M) and 20 mol % acid catalyst. Black bars = aniline, striped bars = heptanamide.

Table 1 Ammonolysis of heptanamides.^a



Entry	NR'R	Conversion	Percent Yield	
			HNR'R	Heptanamide
1		100	95	95
2		100	99	94
3		100	84	84
4 ^b		100	84	95
5		26	32	26
6		100	84	84
7 ^b		62	63	58
8 ^b		42	44	45

^a Ammonolysis of heptanamides (2 mmol) with H_3PO_4 (1 mmol) and ethylene glycol (5 mL). Reaction analyzed by GC with 1,3,5-trimethoxybenzene as the internal standard. ^b Yield determined by ^1H NMR spectroscopy with 1,3,5-trimethoxybenzene as the internal standard.

substrates (Table 1). The parent heptanilide substrate afforded a near-quantitative yield of both products after 15 h (entry 1), and a similarly good result was obtained with *N*-8-quinolinylheptanamide with *N*-8-quinolinylheptanamide (entry 2). The latter result has potential utility in C–H functionalization chemistry, in light of the widespread use of the 8-quinolinyl fragment as a directing group.⁹ Good reactivity was also observed with *N*-(2-bromophenyl)heptanamide (entry 3), 3,5-dimethoxyheptanilide (entry 4), as well as the tertiary amide, 1-(2,3-dihydro-1H-indol-1-yl)-1-heptanamide (entry 8). No side products were observed by GC or NMR spectroscopy. Results with tertiary anilides were variable (entry 5 vs. 6). Decreased yields were obtained with secondary or tertiary amides derived from alkyl amines rather than aryl amines (entries 7 and 8).

The other set of substrates that we examined consisted of anilides bearing different acyl-type groups, including *N*-phenyl aliphatic and aromatic amides, carbamates, *N,N'*-diphenylurea, phthalimide, and toluene sulfonamide (Table 2). Treatment of each of these substrates under the ammonolysis conditions led to excellent yields of aniline in most cases. Exceptions were pivalanilide (entry 3), which is probably less reactive owing to steric effects, and the tosylamide (entry 9), which was unreactive under the reaction conditions. Ammonolysis of *N,N'*-diphenylurea and *N*-phenylphthalimide released aniline in excellent yields (entries 10 and 11).

Table 2 Ammonolytic deprotection of anilide derivatives^a

Entry	Anilide	Aniline Yield (%)	Entry	Anilide	Aniline Yield (%)
1		100	7		95
2		95	8		95
3 ^b		29	9		0
4		94	10		100
5		100	11		91
6		80			

^a anilides (2 mmol) with H₃PO₄ (1 mmol), ethylene glycol (5 mL) and anhydrous ammonia (7-9 M) at 145 °C for 15 h. Aniline yield determined by GC with 1,3,5-trimethoxybenzene as internal standard.

To our knowledge, the results described above represent the first effort to optimize the direct ammonolysis of carboxamides. The use of ethylene glycol, glycerol or another diol as solvents, and the use of a Brønsted or Lewis acid significantly promotes the reaction. The mechanistic basis for the solvent effect is not yet fully understood, but the empirical data suggest that solvent polarity and hydrogen bonding effects are important.

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† Electronic Supplementary Information (ESI) available: Details of experimental protocols, reaction optimization data, and substrate characterization data. See DOI: 10.1039/b000000x/

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