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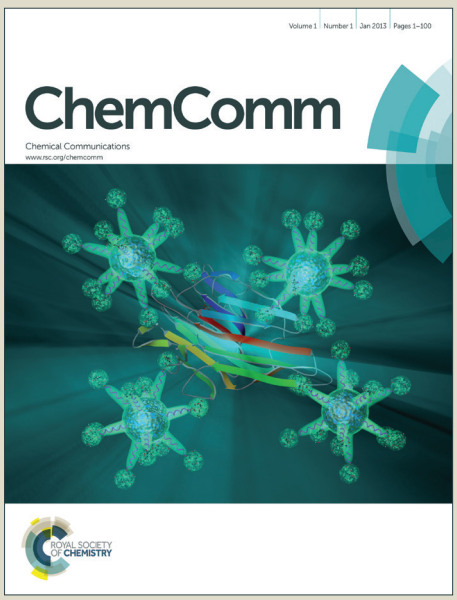

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Cleavage of unactivated amide bonds by ammonium salt-accelerated hydrazinolysis

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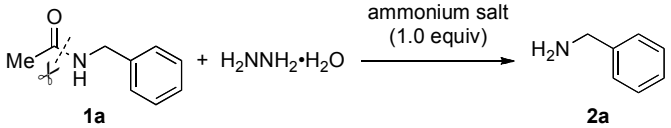
Hydrazinolysis of unactivated amide bonds is significantly accelerated by the addition of ammonium salts. The reactions proceed at 50–70 °C to give amines with broad substrate scope that outperforms existing amide bond cleavage reactions. Application to peptide and amino sugar derivatives is also demonstrated.

Amide is a ubiquitous structural motif in various organic molecules such as peptides, natural products, and pharmaceuticals, because of the high stability of amide bonds.[1] The recent development of catalytic methods, such as C–H activation,[2] hydrogenation,[3] and kinetic resolution,[4] expands the utility of amides as useful directing/protecting groups in organic reactions. In contrast to the utility of amides in organic synthesis, cleavage of amide bonds is less explored due to the high stability of amide bonds, and the most general method to cleave amide bonds is conventional hydrolysis under harsh acidic/basic conditions with limited functional group tolerance.[5] Recent efforts to circumvent the problem have provided several elegant solutions,[6] but these reactions still require anhydrous conditions and/or high reaction temperatures and have limited functional group tolerance. To expand the utility of simple, unactivated amides for the synthesis of organic molecules, the development of general and practical methods to cleave amide bonds under mild conditions is necessary.[7]

To overcome these limitations, we were interested in hydrazinolysis of amide bonds. Hydrazinolysis of activated amide bonds is widely utilized, especially for the removal of phthaloyl groups under mild conditions in Gabriel amine synthesis.[8] Hydrazinolysis of simple unactivated amides is generally very difficult, however, because of the lack of intramolecular assistance during cleavage of the amide bonds, and a high temperature and long reaction time are necessary to provide amine **2** in reasonable yield in most cases.[9] Hydrazinolysis of simple amide bonds under mild conditions was limited to only amino acid derivatives and readily cleavable formamides,[10] and has not been recognized as a general method to cleave simple, unactivated amide bonds because of the limited reactivity of hydrazinolysis under the reported reaction conditions (*vide infra*). To improve the applicability of hydrazinolysis, we hypothesized that the addition of ammonium salts would activate amide bonds and promote hydrazinolysis at a lower reaction temperature similar to the transamidation reaction using ethylenediamine.[11,12] Herein, we report ammonium salt-accelerated hydrazinolysis of unactivated amides using readily available hydrazine monohydrate as the cleaving agent. Reactions proceeded at 50–70°C to provide amines in good yields with broad substrate scope that outperforms existing amide bond cleavage reactions.

To test our hypothesis, we first explored reaction conditions using hydrazine hydrate at 60 °C for 6 h under conventional heating conditions (Table 1). Reactions proceeded only sluggishly under the conditions reported in the previous literature (entries 1[10a] and 2[10b]).[13] By contrast, the addition of ammonium salts significantly accelerated the reaction to provide amine **2a**, and the addition of ammonium iodide showed the highest reactivity (entries 3–5). No reaction proceeded with tetrabutylammonium iodide, suggesting that ammonium salt functions as a proton source (entry 6). Prolonging the reaction time to 24 h gave a satisfactory result (entry 7), and the reaction proceeded even at 50 °C in 89% yield (entry 8). Although conventional heating conditions were sufficient to promote amide bond cleavage as described above, a significant acceleration of the amide bond cleavage was observed under microwave irradiation conditions to give **2a** in 90% yield for 5 h at 50 °C (entry 9).[14]

Table 1 Optimization of reaction conditions



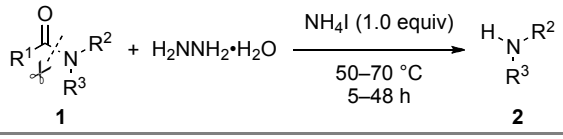
1a **2a**

Entry	Ammonium Salt	Temp. (°C)	*t* (h)	Yield [a] (%)
1	none	60	6	n.d.[b]
2	H_2NNH_2•AcOH[c]	60	6	7
3	NH_4Cl	60	6	35
4	NH_4Br	60	6	45
5	NH_4I	60	6	52
6	$n$$Bu_4NI$	60	6	n.d.[b]
7	NH_4I	60	24	90[d]
8	NH_4I	50	48	89[d]
9[e]	NH_4I	50	5	90[d]

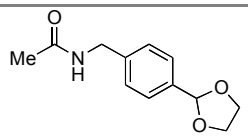
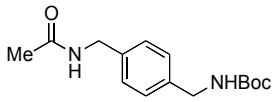
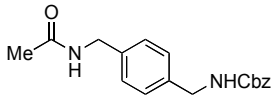
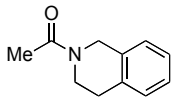
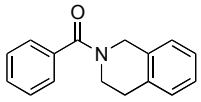
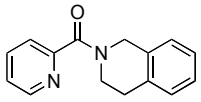
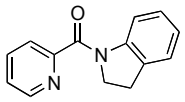
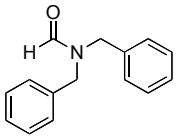
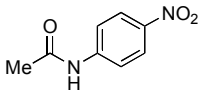
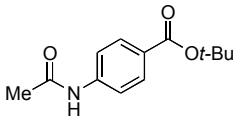
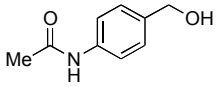
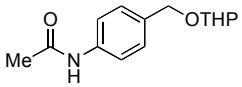
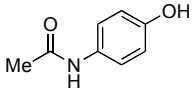
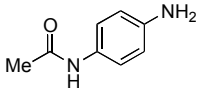
[a] Yield was determined by ^{1}H NMR analysis of the crude mixture. [b] Not detected. [c] 3.0 equiv. of $H_2NNH_2•H_2O$ and AcOH were used in EtOH (1.0 M). [d] Isolated yield. [e] Under microwave irradiation conditions.

With the optimized conditions in hand, we performed hydrazinolysis of various amides **1** (Table 2). The reactions proceeded at 50–70 °C even under conventional heating conditions to give amine **2** in 78–99% yield. Some of the reactions were performed under microwave irradiation conditions to provide amines in a shorter reaction time (entries 3, 5 and 8). Various secondary and tertiary amides were also reacted, and broad functional groups were tolerant under the current hydrazinolysis conditions. Amides **1b**, **1c**, and **1d** having acetonide, *tert*-butoxycarbonyl, and benzyloxycarbonyl functionalities, respectively, also gave products in good yields, indicating the mildness of the current reaction conditions.[13] It is noted that the cleavage of sterically congested formamide **1i** was slow without addition of ammonium iodide (entry 8 in parenthesis), indicating importance of ammonium iodide as additive to accelerate reactions.

Table 2 Scope and limitations of hydrazinolysis of amides

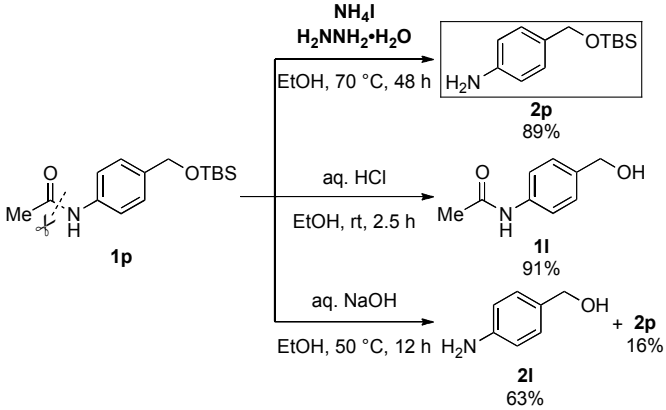


1 **2**

Entry	Amide **1**		Temp (°C)	*t* (h)	Yield (%)[a]
1		**1b**	60	36	78
2[b]		**1c**	70	45	85
3[c]		**1d**	60	4	79
4		**1e**	60	48	92
5[c]		**1f**	70	10	84
6		**1g**	50	36	83
7[b]		**1h**	50	18	85
8[b,c]		**1i**	70	5	92 (26)[d]
9[b]		**1j**	60	42	97
10		**1k**	70	48	84
11		**1l**	50	18	94
12[b]		**1m**	60	45	94
13		**1n**	50	12	97
14		**1o**	50	12	99

[a] Isolated yield. [b] Reaction was performed in EtOH. [c] Under microwave irradiation conditions. [d] Without addition of NH_4I.

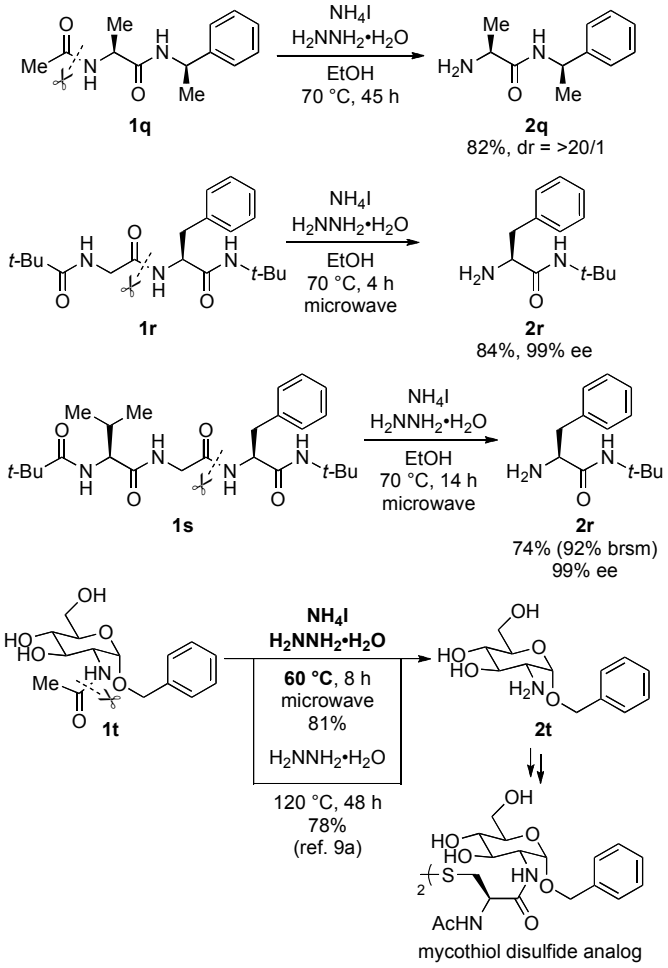
Broad functional group tolerance under the current reaction conditions was further confirmed with amide **1p**, which has an acid- and base-sensitive *tert*-butyldimethylsilyloxy group (Scheme 1). As expected, the desired product **2p** was obtained in 89% yield with retention of the TBS group under our reaction conditions. On the other hand, undesired desilylated product **1l** and **2l** were obtained as major products under conventional acidic and basic hydrolysis conditions.



Scheme 1 Comparison with conventional acidic/basic hydrolysis conditions.

Finally, we applied our reaction conditions to cleave peptide and amino sugar amide bonds (Scheme 2). Selective deacetylation of

alanine derivative **1q** was realized under the current conditions. Furthermore, selective cleavage of the Gly-Phe bond was realized when peptide **1r** and **1s** were exposed to the current reaction conditions to give amine **2r** in 84% and 74% yield (92% based on recovered starting material), respectively, without racemization at the α-position of the phenylalanine residue.[13] The observed site-selectivity was presumably affected by both steric and electronic nature of amide bonds.[13] In addition, this reaction condition was also applied to cleavage of an *N*-acetyl group from amino sugar derivative **1t**. Without the addition of ammonium salt, a high temperature and long reaction time were required to obtain **2t**,[9a] but with ammonium iodide the reaction proceeded at 60 °C in a shorter reaction time under microwave irradiation conditions to give the desired product **2t** in 81% yield.



Scheme 2 Application to peptide and amino sugar derivatives.

In summary, we developed ammonium salt-accelerated hydrazinolysis of unactivated amides. The reactions proceeded by using readily available ammonium iodide and hydrazine monohydrate under mild conditions (50–70 °C without strong acids and bases) with broad substrate generality, including protic functional groups, which is superior to the conventional acidic/basic hydrolysis conditions and recently reported amide bond cleavage reactions. Application to peptide and amino sugar derivatives further confirmed the applicability of our method. Further experiments are underway in our laboratory to gain a detailed understanding of the reaction mechanism and to determine further applications.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental details and characterization data. See DOI: 10.1039/c000000x/

1 W. Mabey, and T. Mill, *J. Phys. Chem. Ref. Data* 1978, **7**, 383.
2 Review of C–H activation: (*a*) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; (*b*) L. Ackermann, R. Vicente and A. R. Kapdi, *Angew. Chem. Int. Ed.*, 2009, **48**, 9792; (*c*) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem. Int. Ed.*, 2009, **48**, 5094; (*d*) O. Daugulis, H.-Q. Do and D. Shabashov, *Acc. Chem. Res.*, 2009, **42**, 1074.
3 Review of hydrogenation: (*a*) K. Gopalaiah and H. B. Kagan, *Chem. Rev.*, 2011, **111**, 4599; (*b*) J.-H. Xie, S.-F. Zhu and Q.-L. Zhou, *Chem. Rev.*, 2011, **111**, 1713; (*c*) T. C. Nugent and M. El-Shazly, *Adv. Synth. Catal.*, 2010, **352**, 753.
4 Review of kinetic resolution: (*a*) E. Busto, V. Gotor-Fernández and V. Gotor, *Chem. Rev.*, 2011, **111**, 3998; (*b*) C. E. Müller, and P. R. Schreiner, *Angew. Chem. Int. Ed.*, 2011, **50**, 6012; (*c*) H. Pellissier, *Adv. Synth. Catal.*, 2011, **353**, 1613.
5 P. G. M. Wuts and T. W. Greene, *Protective Groups in Organic Synthesis,* 4th edn., Wiley-Interscience, Hoboken, 2006, pp. 773–789.
6 For selected recent reactions involving unactivated amide bond cleavage step, see: (*a*) P. R. Sultane, T. B. Mete and R. G. Bhat, *Org. Biomol. Chem.*, 2014, **12**, 261; (*b*) Y. Kita, Y. Nishii, A. Onoue and K. Mashima, *Adv. Synth. Catal.*, 2013, **355**, 3391; (*c*) Y. Kita, Y. Nishii, T. Higuchi and K. Mashima, *Angew. Chem. Int. Ed.*, 2012, **51**, 5723; (*d*) E. Balaraman, B. Gnanaprakasam, L. J. W. Shimon and D. Milstein, *J. Am. Chem. Soc.*, 2010, **132**, 16756; (*e*) N. A. Stephenson, J. Zhu, S. H. Gellman, and S. S. Stahl, *J. Am. Chem. Soc.*, 2009, **131**, 10003; (*f*) S. G. Koenig, C. P. Vandenbossche, H. Zhao, P. Mousaw, S. P. Singh and R. P. Bakale, *Org. Lett.*, 2009, **11**, 433 and references therein.
7 For selected recent examples of facile cleavage of *strained* amide bonds, see: (*a*) J. Aubé, *Angew. Chem. Int. Ed.*, 2012, **51**, 3063; (*b*) M. Hutchby, C. E. Houlden, M. F. Haddow, S. N. G. Tyler, G. Lloyd-Jones and K. I. Booker-Milburn, *Angew. Chem. Int. Ed.*, 2011, **51**, 548; (*c*) K. Tani and B. M. Stoltz, *Nature*, 2006, **441**, 731.
8 J. March, *Advanced Organic Chemistry: Reactions, Mechanisms and Structures,* 5th edn.; John Wiley & Sons: New York, 2001; p. 513 and references cited therein.
9 Selected examples of hydrazinolysis of unactivated amides: (*a*) M. J. G. Stewart, V. K. Jothivasan, A. S. Rowan, J. Wagg and C. J. Hamilton, *Org. Biomol. Chem.*, 2008, **6**, 385; (*b*) K. Fukatsu, O. Uchikawa, M. Kawada, T. Yamano, M. Yamashita, K. Kato, K. Hirai, S. Hinuma, M. Miyamoto and S. Ohkawa, *J. Med. Chem.*, 2002, **45**, 4212; (*c*) L. H. Jones, L. J. Altobell III, M. T. MacDonald, N. A. Boyle, P. Wentworth, Jr., R. A. Lerner and K. D. Janda, *Angew. Chem. Int. Ed.* 2002, **41**, 4241; (*d*) S. Knapp, S. Gonzalez, D. S. Myers, L. L. Eckman and C. A. Bewley, *Org. Lett.*, 2002, **4**, 4337.

10 (*a*) D. D. Keith, J. A. Tortora and R. Yang, *J. Org. Chem*., 1978, **43**, 3711; (*b*) R. Geiger and W. Siedel, *Chem. Ber.*, 1968, **101**, 3386; (*c*) M. Miyamoto, Y. Kawamatsu, M. Shinohara and Y. Ueno, *Yakugakuzasshi*, 1961, **81**, 439.
11 Y. Shimizu, H. Morimoto, M. Zhang and T. Ohshima, *Angew. Chem. Int. Ed*., 2012, **51**, 8564.
12 Although addition of hydrazinium sulfate have been reported for the analysis of peptide sequences, these reaction conditions require *anhydrous* hydrazine and not widely utilized in the field of organic synthesis; see: J. H. Bradbury, *Nature*, 1956, **178**, 912.
13 See Electronic Supplementary Information (ESI) for detail.
14 Safety testing consisting of DSC testing of reaction mixtures was performed. No significant barriers were found to progression of the reaction (50–70 °C) and an exothermic process started at about 160 °C (calorific value: <100 J/g, activation energy: ca. 700 kJ/mol).

