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Direct Synthesis of β-Aminoketones from Amides via Novel Sequential Nucleophilic Substitution/Michael Reaction†

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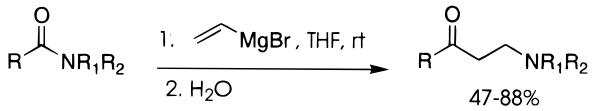
ABSTRACT

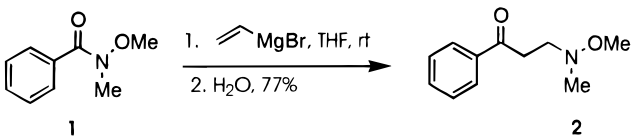


The synthesis of β-aminoketones from amides can be achieved in a process consisting of sequential nucleophilic substitution at the carbonyl group by vinylmagnesium bromide followed by Michael reaction after quench of the first reaction by water.

Sequential transformations in organic chemistry have both theoretical and practical importance.[1] The pathways available for molecules once they are activated under certain conditions widen the arsenal of new reactions and lead to a better understanding of the mechanistic aspects of organic reactions. The utilization and optimization of self-controlled consecutive processes can offer advantages over the stepwise transformations by increasing synthetic efficiency, as well as by saving time, reagents, and waste.

It is well known that amides react with organometallic reagents to give ketones[2,3] by nucleophile substitution of the amine functionality. However, we wish to report that reactions of amides and vinylmagnesium bromide followed by quenching with water afforded β-aminoketones.[4] An illustrative case is shown in Scheme 1 for the conversion of Weinreb amide **1** to the phenyl β-aminoethylketone **2**.

Scheme 1



1 **2**

In a preliminary assessment of the generality of this reaction, we tested several amides in the reaction with vinylmagnesiun bromide followed by water quench as summarized in Table 1.[5] The Weinreb amides of aromatic and heteroaromatic carboxylic acids provided corresponding phenylaminoketone (entry 1) and pyridylaminokeones (entries 2 and 3) in good yields. The electronic nature of the aromatic ring does not seem to be of critical importance for the outcome of the reaction as pyridinecarboxamides with electron-withdrawing (entry 2) and electron-donating (entry 3) groups gave the corresponding β-aminoketones in comparable yields. We have also shown that the Weinreb amide

† Dedicated to Professor Stephen Hanessian on the occasion of his 65th birthday.

(1) For a discussion of sequential transformations in organic chemistry, see: (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Bunce, R. A. *Tetrahedron* **1995**, *48*, 13103. (c) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131. (d) Posner, G. H. *Chem Rev.* **1986**, *86*, 831.

(2) For selected examples, see: (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815. (b) Olah, G. A.; Prakash, S, G. K. S.; Arvanaghi, M. *Synthesis* **1984**, 228.

(3) For a review on the chemistry of the Weinreb amides, see: Sibi, M. P. *Org. Prep. Proced. Intl.* **1993**, *25*, 15.

(4) Presented at the ACS National Meeting in New Orleans, LA, August 22−26, 1999; Abstract 513 ORG.

(5) **General Procedure for the Sequential Transformation of Amides to β-Aminoketones:** To a solution of amide **1** (2.18 g, 13.2 mmol) in dry THF (20 mL) at 0 °C was added a 1 M solution of vinylmagnesium bromide (14.5 mL, 14.5 mmol) in THF within 1 min. After 10 min the mixture was allowed to attain ambient temperature and was stirred for 1 h. The mixture was quenched with water (15 mL) and after 15 min diluted with ethyl acetate and washed twice with water. Organic layer was separated, concentrated, and chromatographed on SiO_2 (20% EtOAc−hexanes) to afford **2** (2.0 g, 77%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (m, 2H), 7.58−7.40 (m, 2H), 3.50 (s, 3H), 3.28 (t, 2H, J = 4.2 Hz), 3.10 (t, 2H, J = 4.2 Hz), 2.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.6, 136.7, 132.7, 128.2, 127.7, 59.6, 55.2, 44.8, 35.9; HRMS calcd for $C_{11}H_{16}NO_2$ 194.1181, found 194.1183.

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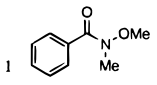
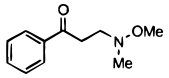
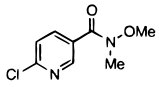
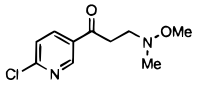
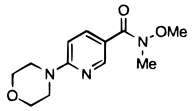
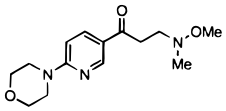
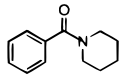
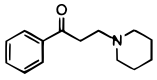
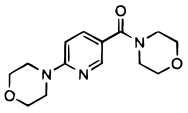
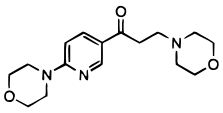
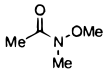
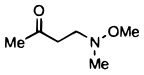
Table 1. Sequential Transformation of Amides to β-Aminoketones

Entry	Amide	Product[a]	Isolated Yield (%)
1			77
2			77
3			88
4			54
5			47
6			66

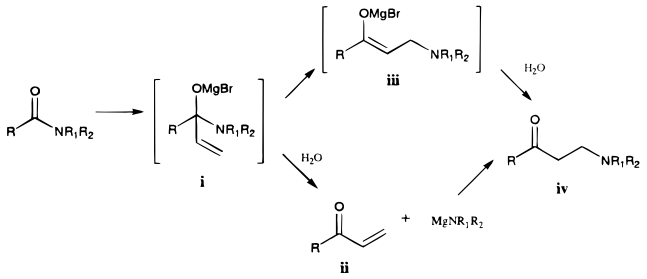
[a]The reaction time for the entries 1-3 and 6 is 1h, for the entries 4 and 5 - 6h.

of the acetic acid can also undergo a sequential transformation nucleophilic substitution/Michael reaction (entry 6) to give methyl β-aminoethylketone. That result indicated the potential for utilizing aliphatic carboxamides in this procedure. The piperidine and morpholine pyridinecarboxamides (entries 4 and 5) are examples of starting materials other than Weinreb amides. Both amides underwent sequential transformation albeit in moderate yields.

The most common methods for synthesis of β-aminoketones, useful synthetic intermediates in organic chemistry, include alkylation of amines by β-haloalkyl ketones, Michael reaction between vinyl ketones and amines,[6] and Mannich reaction of methyl ketones with amine and paraformaldehyde.[7] The procedure described in this paper utilizes stable and readily available amides as starting materials for the direct synthesis of β-aminoketones.[8] The formation of the products, β-aminoketones, can formally be explained by the sequence of a two-step vinyl nucleophile substitution at the carbonyl group followed by a Michael reaction. To the best of our knowledge there is only one report on this type of sequential process in which unstable β-aminoketone intermediates from the reaction between amide and cyclopropenyllithium were observed and characterized by ^{1}H NMR.[9]

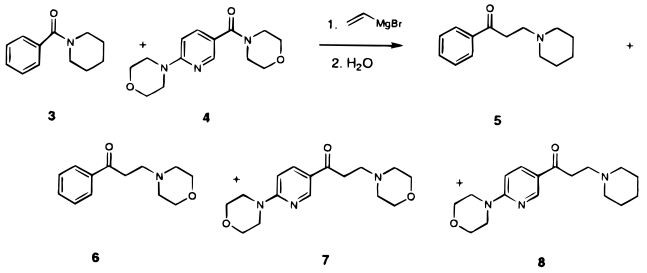
The mechanism of the sequence as shown in Scheme 2 includes formation of the well-known tetrahedral intermediate

Scheme 2

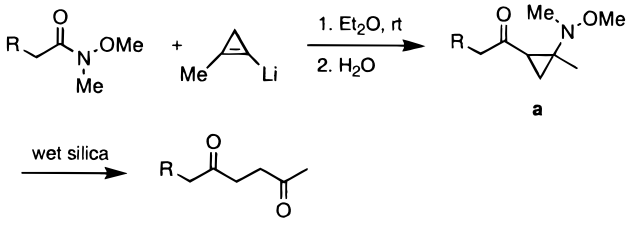


i in the first step. The latter can undergo hydrolysis after the quench to provide vinylketone **ii** which in situ reacts with magnesium amide to give β-aminoketone **iv**. However, there is a possible pathway that includes intramolecular formation of enolate **iii** that would give ketone **iv** after the quench. To clarify the mechanism of the second step of our sequential process, we performed the following experiments. The mixture of the amides **3** and **4 (**Scheme 3), which have very

Scheme 3



similar reactivities, was subjected to a reaction with vinylmagnesium bromide followed by the water quench using the standard conditions. Analysis of the product mixture by GC-MS indicated the formation of all four possible products **5**−**8**. This result eliminates the possibility of the pathway consisting of the intramolecular rearrangement of the tetrahedral intermediate **i** to the enolate **iii**. Indeed, in such a case only



(6) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992; p 114.

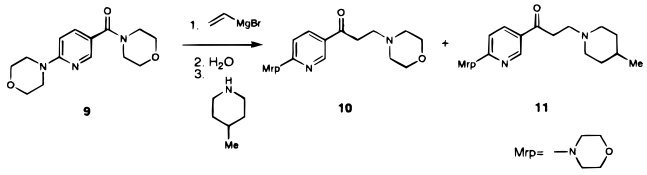
(7) Tramontini, M. *Synthesis* **1973**, 703.

(8) For selected applications of β-aminoketones in the synthesis of natural products and biologically active compounds, see: (a) Buchi, G.; Gould, S. J.; Naf, F. *J. Am. Chem. Soc*. **1971**, *93*, 2492. (b) Takahashi, K.; Shimizu, S.; Ogata, M. *Synth. Commun*. **1987**, *17*, 809. (c) Ogata, M.; Matsumoto, H.; Kida, S.; Shimizu, S.; Tawara, K.; Kawamura, Y. *J. Med. Chem*. **1987**, *30*, 1497.

(9) Wickberg and co-workers described the formation of unstable β-aminoketone **a** from the reaction of the Weinreb amide and methylcyclopropenyllithium en route to 1,4-diketones. Bergman, R.; Nilsson, B.; Wickberg, B. *Tetrahedron Lett*. **1990**, *31*, 2783.

"self-products" **5** and **7** would be observed. To confirm this conclusion we performed a second experiment (Scheme 4).[10]

Scheme 4



The reaction between morpholine amide **9** and vinylmagnesium bromide was quenched with water, and then 2 equiv of 4-methylpiperidine was immediately added after the quench. The product mixture contained both morpholinoketone **10** and piperidinoketone **11**. Since the formation of **11** would not be possible if the enolate **iii** pathway were operable, the mechanism of the second step would most likely be a Michael reaction between vinyl ketone **ii** and in situ formed magnesium amide.

In summary, a novel sequential transformation consisting of substitution at the carbonyl group by a vinyl nucleophile/Michael reaction has been discovered. This process utilizes stable and readily available amides as starting materials and provides an easy access to β-aminoketones. The possibility of preparing β-aminoketones with variable amino groups from one common starting amide was also noted. Results of the last finding and further details regarding the scope and limitations of this sequential process will be reported in due course.

Acknowledgment. The author thanks Professor Peter Beak for helpful and stimulating discussions.

Supporting Information Available: Full characterization data for β-aminoketones as well as starting compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The formation of the enolate **iii** (Scheme 2) could also be envisioned by bimolecular reaction of the tetrahedral internediate **i**. However, the experiment outlined in Scheme 4 ruled out that possibility.