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A facile one-pot synthesis of acyclic β-enamino ketones, an important class of versatile synthetic intermediates

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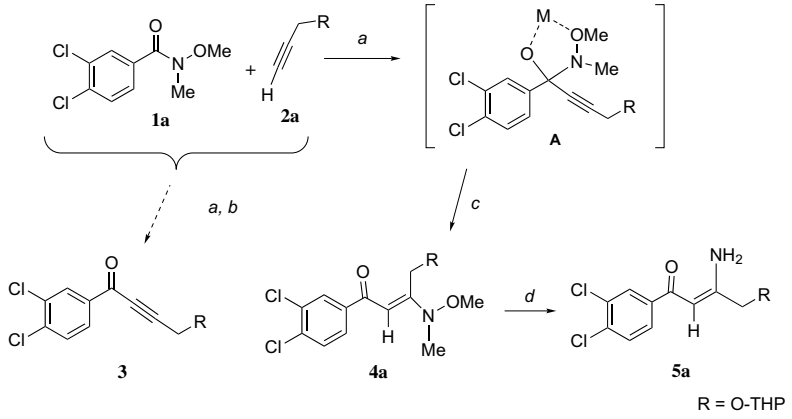
Abstract—A one-pot sequential process consisting of nucleophilic substitution of the lithiated acetylides with Weinreb amides followed by a Michael reaction of the extruded *N*-methoxy-*N*-methylamine after quenching with saturated NH_4Cl, provided β-enamino ketones in high yield and in a single geometrical isomeric form. It has been demonstrated that this method is applicable to a wide variety of such amides and to different acetylides.

A long-standing problem in organic synthesis has been the lack of an effective, clean reduction method of carboxylic acid derivatives to their corresponding aldehydes without over-reduction. Weinreb's group has solved this problem in recent years via the use of the corresponding *N*-methoxy-*N*-methylamide (Weinreb amide) as the reduction precursor. Origin of such control has been attributed to a tetrahedral chelate (as shown in **A**, Scheme 1) involving the –OMe group of the substrate amide with the metal cation, which prevents further reduction.[1] This concept has been also extended to carbon nucleophiles for ketone formation. While use of this methoxyamine segment in regulating nucleophilic attack is the key to prevent over-reduction



Scheme 1. Reagents and condition: (a) Li-HMDS, THF, −10 °C to +10 °C; (b) dilute HCl; (c) saturated NH_4Cl; (d) prolonged stirring.

Keywords: β-Enamino ketones; Weinreb amide.
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or reaction, its role in the post-reaction mixture has not been fully explored. This Letter is a subject of such work, which describes a facile preparation of β-enamino ketones, a versatile class of synthetic intermediates.

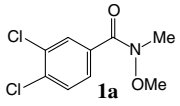
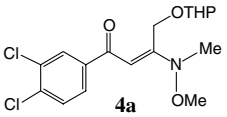
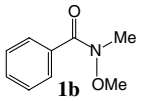
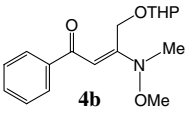
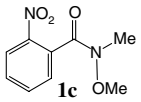
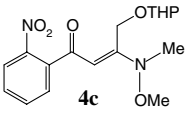
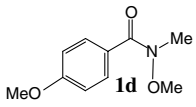
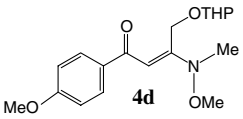
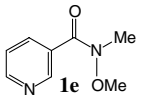
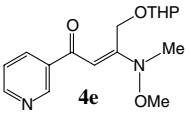
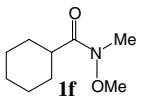
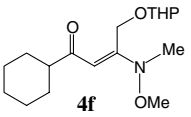
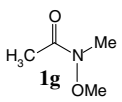
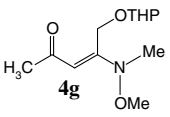
We were interested in preparing a propargylic ketone bearing an acid sensitive tetrahydropyranyloxy (OTHP) functionality (**3**, R = OTHP, Scheme 1) via lithium acetylide addition to Weinreb amide **1a**. When this reaction was carried out following standard conditions (LiHMDS added to a mixture of **1a** and **2a** in THF at −10 to +10 °C followed by a saturated NH_4Cl quench), we were surprised to find none of the expected acetylenic ketone **3**. The major product formed in this reaction was characterized as the isomerically pure (*E*) *N*-methoxy-*N*-methyl-β-enamino ketone **4a**.[2] This unwanted reaction product was considered to arise from the Michael addition of *N*-methoxy-*N*-methylamine with the desired acetylenic ketone **3**. We were intrigued by the ease of which this Michael addition took place and the potential synthetic utility of β-enamino ketone products.

To test the usefulness of this synthetic method, we prepared a wide variety of Weinreb amides (**1a**–**g**) and reacted each with lithium acetylide of **2a** followed by a saturated NH_4Cl quench. The results are recorded in Table 1. In all cases, high yields of the (*E*) *N*-methoxy-*N*-methyl-β-enamino ketones were obtained. The electronic influence of the substituents on the aromatic ring seem to have little or no impact on the yield and nature of the reaction (entries 1–4). Heterocyclic (entry 5), alicyclic and aliphatic amides (entries 6 and 7) also led to moderate to high yields, clearly demonstrating the versatility of this synthetic method. We also examined several lithiated acetylides and found that good yields were obtained as well (Table 2). 3,4-Dichlorocarboxamide (**1a**) was used as a model substrate, and reacted with different lithiated acetylides, derived from the corresponding acetylenes (entries 1–4). In all cases, the yields were high and a single geometrical isomer was formed.

While this work was in progress, we came across a similar type of sequential Micheal addition product involving *N*-methoxy-*N*-methylamine (B) but with a vinylic system (Fig. 1) to generate β-amino ketones.[3]

While continuing to explore the scope and limitations of preparing *N*-methoxy-*N*-methyl-β-enamino ketones,[4] we found that prolonged stirring (48–72 h) of the NH_4Cl quenched reaction mixture led to an exchange of the amines and resulted in the generation of β-enamino ketones (Table 3). Thus the *N*-methoxy-*N*-methylamine unit in the substrates does not remain as an imposing structural feature, but rather can be exchanged with other amines to introduce novel amine segments to the vinylic system. More interestingly, a reversal in double bond configuration was noticed in all cases (Table 1 vs Table 3). The *Z*-isomer was obtained, presumably via an addition elimination process to form the thermodynamically more stable product that enjoys an intramolecular hydrogen bond between the amino group and the β-carbonyl group (Fig. 1, **5a**–**k**).

Table 1. One-pot sequential transformation of Weinreb amides (**1a**–**g**) to enamino ketones (**4a**–**g**) via the addition of propargyl-Li (from **2a**) followed by satd NH_4Cl quench

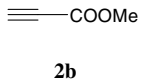
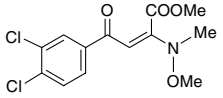
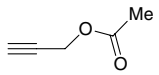
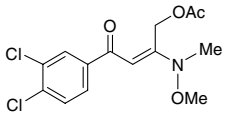
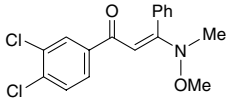
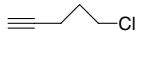
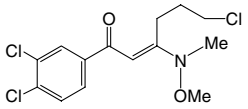
Entry	Amide[a]	Product[b]	Yield[c] (%)
1	 **1a**	 **4a**	86
2	 **1b**	 **4b**	86
3	 **1c**	 **4c**	72
4	 **1d**	 **4d**	85
5	 **1e**	 **4e**	93
6[d]	 **1f**	 **4f**	81
7	 **1g**	 **4g**	65

[a] For a general preparation of the Weinreb amides see Ref. 9.
[b] For a general procedure see Ref. 10, a single geometrical isomer was obtained in each case, NOE experiment for **4a** indicated *E* configuration for the double bond, for **4b**–**g** double bond configuration was assumed to be *E*.
[c] Isolated crude yield, purity was >95% in each case.
[d] The second addition step was carried out at 40 °C.

In general, the synthesis of β-enamino ketones is not straightforward. Metal mediated reduction of oxazolines[5] and reaction of 1,3-diketones with amines are the major synthetic methods to generate them. Recently, Muller et al. have shown a sequential protocol which uses the reaction of an acid chloride and acetylenes under Sonogashira condition ($Pd(PPh_3)_3Cl_2$, CuI) followed by an attack of primary or secondary amines to generate these important intermediates.[6] In contrast to these methods, our present method is extremely simple, versatile and generates high yields of isomerically pure β-enamino ketones which are strategic precursors useful in preparing a wide variety of compounds.

Mechanistically, the formation of the *N*-methoxy-*N*-methyl-β-enamino ketone[7] can be explained by a

Table 2. The products from the addition of different lithiated acetylides (**2b–e**) with 3,4-dichlorocarboxamide (**1a**) followed by satd NH_4Cl quench

Entry	Acetylene[a]	Product[b]	Yield[c] (%)
1	 **2b**	 **4h**	77
2	 **2c**	 **4i**	83
3	 **2d**	 **4j**	85
4	 **2e**	 **4k**	83

[a] LiHMDS was used as the base to generate the corresponding acetylides.
[b] Based on **4a**, the configuration of the double bond was assumed to be *E*.
[c] Isolated crude yield, purity was >95% in each case.

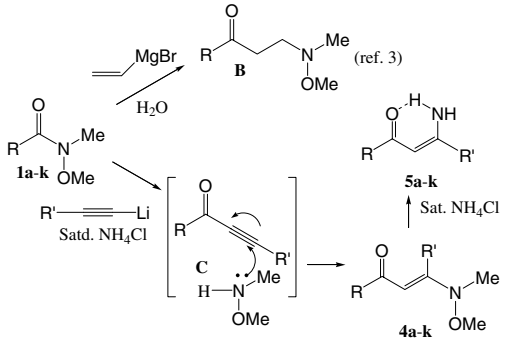
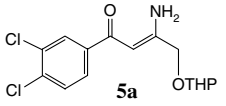
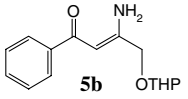
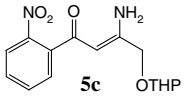
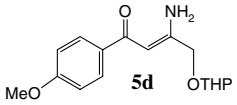
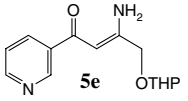
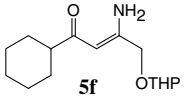
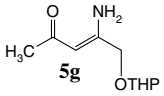
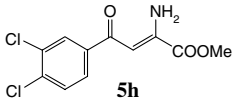
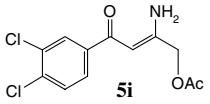
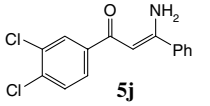
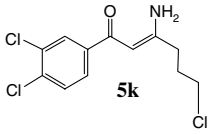


Figure 1.

three-step process.[8] The first step involves a nucleophilic substitution of a lithium acetylide to a Weinreb amide followed by a second step generation of the propargylic ketone via quenching of the tetrahedral intermediate. In the third step, a Michael addition occurs between the liberated *N*-methoxy-*N*-methyl amine and the ketone (Fig. 1). Evidence for this mechanism comes from monitoring the reaction by ^{1}H NMR. When the reaction was carried out with lithium phenyl acetylide and **1a**, the acetylenic ketone was observed after immediate quenching (satd NH_4Cl) and workup. Further monitoring by ^{1}H NMR showed the eventual formation of the corresponding β-enamino ketone **4j**.

In a separate experiment we reacted *N*-methoxy-*N*-methylamine with acetylenic ketone **3** and observed

Table 3. One-pot synthesis of β-enamino ketones: prolonged stirring of the quenched propargylation reaction mixture

Entry	Amide	Product[a]	Yield[b] (%)
1	**4a**	 **5a**	94
2	**4b**	 **5b**	[c]
3	**4c**	 **5c**	[c]
4	**4d**	 **5d**	83
5	**4e**	 **5e**	83
6	**4f**	 **5f**	81
7	**4g**	 **5g**	91
8	**4h**	 **5h**	77
9	**4i**	 **5i**	83
10	**4j**	 **5j**	85
11	**4k**	 **5k**	83

[a] NOE experiment and X-ray structure determination for **5a** proved the configuration of the double bond to be *Z*, for other enamino ketones the double bond configuration was assumed to be *Z*, for a general procedure see Ref. 11.
[b] Isolated crude yield.
[c] Quantitative.

clean formation of the corresponding β-enamino ketone. The origin of selective formation of a single geometrical isomer, however, is not clearly understood. We presume that *N*-methoxy-*N*-methylamine dictates the selective protonation of the Michael addition intermediate, resulting in the *E* geometrical isomer.

In conclusion, we have demonstrated a mild and efficient synthetic method to transform carboxamides to β-enamino ketones in one reaction flask. Further potential of this synthetic methodology is currently ongoing and will be reported.

Acknowledgements

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References and notes

1. (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815; see (b) Sibi, M. P. *Org. Prep. Proced. Int.* **1993**, *25*, 15.
2. (a) Choudhury, A; Grimm, J. S.; Jones, T. K.; Liang, J. T.; Mani, N; Sorgi, K. L. WO 2005/005393; (b) The content of this manuscript and related work were presented at the following symposiums: (1) A facile one-pot synthesis of β-enamino ketones: A masked diketone with distinct reactivity difference. Choudhury, A; Grimm, J. S.; Sorgi, K. L; Xiao, T; Breslav, M; Xu, D.; Presented at the 230th ACS National Meeting, Washington, DC, United States, August 28–September 1, 2005. (2) Novel and highly regioselective synthesis of substituted pyrazoles. Grimm, J. S.; Callahan, R.; Choudhury, A.; Segmuller, B.; Sorgi, K. L.; Xiao, T; Xu, D. Presented at the 229th ACS National Meeting, San Diego, CA, United States, March 13–17, 2005; (c) Very recently, we came across a communication, which describes synthesis of a substrate similar to **4a** via analogous method as disclosed in our patent application, WO 2005/005393 (Persson, T., Nielsen, J. *Org. Lett.* **2006**, *8*, 3219).
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9. Synthesis of 3,4-dichloro-*N*-methoxy-*N*-methyl-benzamide (**1a**): *N*,*O*-Dimethylhydroxylamine hydrochloride (1.48 kg, 14.88 mol) was suspended in EtOAc (16 L) and warmed to 35 °C. A solution of 3,4-dichlorobenzoyl chloride (3.00 kg, 13.88 mol) in EtOAc (8 L) was added, followed by addition of diisopropylethyl amine (5.45 ml, 31.2 mol) while maintaining the temperature below 40 °C. The reaction suspension was stirred for 1 h. When TLC analysis confirmed reaction completion by the disappearance of starting material, the reaction mixture was cooled to room temperature and water (10 L) was added to achieve a two-phase clear solution. After removing the aqueous layer, the organic layer was dried (Na_2SO_4) and concentrated to afford **1a** (3.38 kg) as an oil. Upon sitting at room temperature the product crystallized. HPLC area% purity 99.3%. mp: 43.2 °C. Yield: quantitative. IR (KBr pellet): 3445.0, 3258.0, 3091.6, 2981.4, 2945.5, 1942.4, 1645.6, 1588.6, 1557.4, 1462.9, 1414.5, 1368.0, 1386.2, 1262.0, 1209.0, 1130.0, 1112.5, 1071.8, 1030.9, 100.9, 893.8 cm^{-1}. ^{1}H NMR ($CDCl_3$): 7.8 (d, 1H, $J = 2$ Hz), 7.54 (dd, 1H, $J = 2$ and 8.4 Hz), 7.46 (d, 1H, $J = 8.3$ Hz), 3.54 (s, 3H), 3.34 (s, 3H). ^{13}C NMR ($CDCl_3$): 167.2, 135.0, 133.9, 132.4, 130.7, 130.2, 127.9, 61.5 and 33.0.
10. General procedure for the sequential transformation of the amides to β-enamino ketones: To a solution of amide **1a** (0.79 g, 3.33 mmol) and propargyl-THP (0.48 mL, 3.4 mmol) in dry THF (3 mL), lithium hexamethyldisilazide (LiHMDS, 3.4 mL, 1 M/THF) was added between −10 and +10 °C. The reaction mixture was stirred for 1 h at that temperature range and quenched with 10 mL of saturated NH_4Cl. The mixture was warmed to ambient temperature and 10 mL of EtOAc was added to facilitate the layer separation. The organic layer was separated and dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated in vacuum and dried at high vacuum to afford 1.07 g (86%) of **4a** as a thick oil. Compound **4a**: MS (ES+): mass calcd for $C_{17}H_{21}Cl_2NO_4$, 373.08; *m*/*z* found, 374.1 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$): 7.95 (d, $J = 2.1$ Hz, 1H), 7.69 (dd, $J = 8.4$, 2.1 Hz, 1H), 7.44 (d, $J = 8.3$ Hz, 1H), 6.12 (s, 1H), 5.13 (d, $J = 12$ Hz, 1H), 4.79–4.77 (m, 1H), 4.76 (d, $J = 11.5$ Hz, 1H), 3.70 (s, 3H), 3.88–3.86 (m, 1H), 3.30 (s, 3H), 1.83–1.50 (m, 3H), 1.49–1.21 (m, 4H).
11. Prolonged stirring of the reaction mixture after the quench with saturated NH_4Cl (Ref. 10) for 48–72 h generated cleanly the β-enamino ketone **5a** in 94% yield (Table 3, entry 1). (ES+): mass calculated for $C_{14}H_{15}Cl_2NO_3$, 329.06; *m*/*z* found, 330.1 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$): 10.2 (br s, 1H), 8.19 (m, 1H), 7.77 (d, $J = 2$ Hz, 1H), 7.47 (d, $J = 2.8$ Hz, 1H), 6.33 (br s, 1H), 5.62 (s, 1H), 4.68–4.66 (m, 1H), 4.45 (d, $J = 15$ Hz, 1H), 4.4 (d, $J = 15$ Hz, 1H), 3.91–3.83 (m, 1H), 3.60–3.53 (m, 1H), 3.30 (s, 3H), 2.0–1.6 (2 m, 6H).