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Synthesis of *N*-Methoxy-*N*-methyl-β-enaminoketoesters: New Synthetic Precursors for the Regioselective Synthesis of Heterocyclic Compounds

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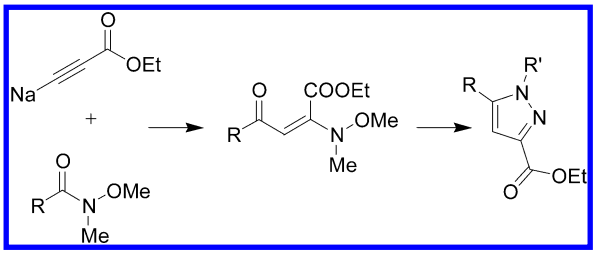
ABSTRACT



Weinreb amides react with the lithium or sodium acetylide of ethyl propynoate in a hitherto unexplored acyl substitution–conjugate addition sequence to furnish (*E*)-*N*-methoxy-*N*-methyl-β-enaminoketoesters. This approach provides a diverse entry to densely functionalized heterocyclic compounds, including pyrazoles through regioselective cyclocondensations with hydrazines in a microwave-assisted reaction.

Design and synthesis of bioactive small molecules is of key importance in medicinal chemistry and chemical biology. Equally, drug discovery has utilized and benefited from the wide chemical space that natural products offer.[1] In the early 1990s, combinatorial chemistry was introduced to provide large diverse collections of molecular entities through a minimal number of unit operations and manipulations.[2] Today, combinatorial chemistry continues to evolve, and the assimilation of natural product structures is attracting increasing attention.[3] In combinatorial chemistry, it is important to limit the number of synthetic operations unless the interconversion of functional groups or fusion of building blocks is highly optimized, such as for solid-phase peptide or oligonucleotide synthesis.[4]

We have focused on the design and synthesis of arrays of a range of different small heterocyclic molecules, herein exemplified by the synthesis of pyrazoles from β-enaminoketoesters. The pyrazole scaffold was selected since it is well-represented in bioactive structures,[5] including pyrazoles

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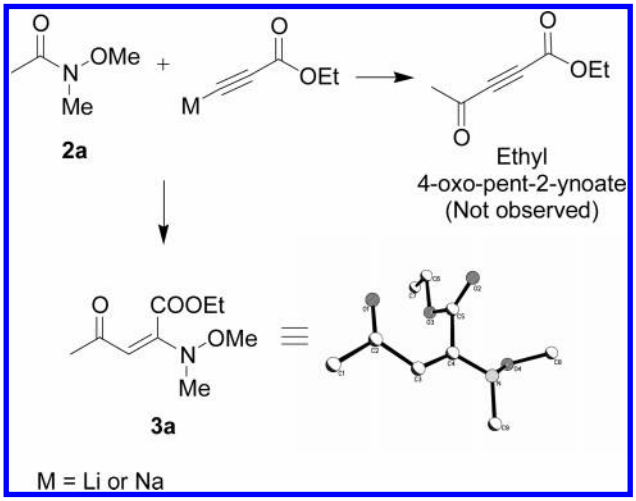
having an amide or ester functionality installed in the 3-position.[6] Numerous syntheses of such 3-carboxy-functionalized pyrazoles have been reported,[7] but the most prevalent approach relies on the Knorr pyrazole synthesis.[8] This classic condensation reaction between α,γ-diketoesters and hydrazines is hampered by low regioselectivity.[9,10] Furthermore, the preparation of α,γ-diketoesters from methyl ketones limits the diversity of side chains that may be introduced around the heterocyclic core.

A regioselective approach to heteroaromatic structures, such as pyrazoles, although less established, is the analogous addition of hydrazines to an acetylenic ketone.[11] This strategy also works well for acetylenic ketoesters resulting in ester-functionalized pyrazoles.[12] However, acetylenic ketoesters are scarce synthetic intermediates commonly prepared from the corresponding aldehydes in two steps.[13] Even though direct addition of activated carboxylic acids to alkynes has been well-documented over the last few decades,[14] to date, the only useful addition to alkyl propynoates is via a potentially explosive silver acetylide.[15] Moreover, in our experience, acid chlorides (PhCOCl and AcCl) add to the analogous lithium acetylide in low yield (Supporting Information). Thus, the need for methodology that gives direct access to acetylenic ketoesters or related structures with equal reactivity from activated acids is apparent. Hitherto, few reports[16] describe the reaction of Weinreb amides with alkyl propynoates.

When performing this reaction with the lithium acetylide derived from ethyl propynoate (**1**), *N*-methoxy-*N*-methylacetamide (**2a**) gave the corresponding β-enaminoketoester **3a** and *not* the expected ethyl 4-oxo-pent-2-ynoate. [LHMDS (2.5 mmol, 1.0 M in THF) added to ethyl propynoate (2.25 mmol) in THF (2.5 mL) at −78 °C then addition of MeCON(OMe)Me (2.5 mmol, 5.0 M in THF). Quenching by addition of aqueous HCl (1.0 M) after 96 h. The isolated yields of **3a** and **4a** after flash chromatography were 25 and 32%, respectively.]

Tertiary enaminones, such as **3a**, preferentially adopt *E*-geometry,[17] whereas primary and secondary enaminones, such as **5** and **6**, exist predominantly in the *Z*-form, energetically favored by intramolecular hydrogen bonding. In accordance with this, only one geometric isomer could be detected in the crude reaction mixture, and the *E*-stereochemistry of β-enaminoketoester **3a** was confirmed by an X-ray crystal structure determination (Scheme 1) after purification.

Scheme 1. Reaction of Weinreb Amide **2a** with Ethyl Propynoate (**1**) and ORTEP Plot of the Molecular Structure of **3a**



The reaction rate was very dependent on the polarity of the solvent. Thus, in toluene, the observed reaction was much slower than that in THF, and no reaction was observed in hexane. The reaction time required for full conversion was shortened considerably from the initial 96 to 1.5 h by raising the temperature of the reaction mixture from −78 to −40 °C and by employing the *sodium* acetylide instead of lithium acetylide. The observed reactivity pattern for the sodium acetylide of ethyl propiolate is contradictory to Herrmann et al.[18] and Midland et al.[19] who reported that lithium salts of alkyl propionates add to ketones in higher yield than their sodium counterparts, due to the higher basicity of the latter. The basicity (HSAB) had less significance in the reaction with a Weinreb amide.

To test the generality of this reaction and explore the potential of the technology in array and combinatorial

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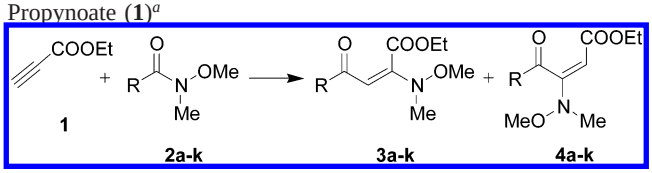
synthesis, a series of Weinreb amides **2b**−**k** were employed under the same conditions as for Weinreb amide **2a** (Table 1).

Table 1. Reaction of Weinreb Amides (**2a**−**k**) with Ethyl Propynoate (**1**)[a]



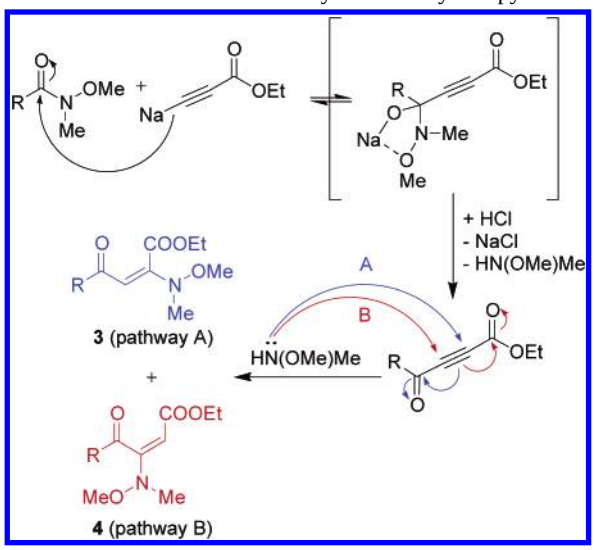
entry	**2**	R (enaminoketoester)	yield **3**/**4** (%)[b]
1	**a**	Me	31/33
2	**b**	Et	41/34
3	**c**	Bn	44/30
4	**d**	$Ph(CH_2)_2$	34/33
5	**e**	*i*-Pr	52/36
6	**f**	*t*-Bu	*c*
7	**g**	Ph	96/−
8	**h**	$4\text{-}NO_2\text{−}C_6H_4$	75/−
9	**i**	$4\text{-}CH_3O\text{−}C_6H_4$	72/−
10	**j**	$2,4\text{-}(CH_3O)_2\text{−}C_6H_3$	*c*
11	**k**	$2,4\text{-}Cl_2C_6H_3$	60/−

[a] General method: NaHMDS (2.0 mmol, 1.0 M in THF) added to ethyl propynoate (2.0 mmol) in THF (2.0 mL) at −78 °C then addition of RCON(OMe)Me (1.0 mmol), → −40 °C. Quenching by aqueous HCl (1 M). [b] Isolated yields after flash chromatography. [c] No reaction was observed.

In all cases, the total enaminoketoester yield exceeded 60%. Weinreb amides with less substituted α-carbons displayed low selectivity and resulted in formation of α-enaminoketoesters **4a**−**e** in addition to *β*-enaminoketoesters **3a**−**e** (Table 1, entries 1−5). Bulky substituents on the other hand, such as *tert*-butyl (**2f**, Table 1, entry 6) and 2,4-dimethoxyphenyl (**2j**, Table 1, entry 10), were not suitable starting materials, suggesting a steric effect. However, the high selectivity observed for **3g**−**i** and **3k** (Table 1, entries 7−9 and entry 11) indicates additional electronic contribution from aryl substituents which, without being particularly bulky, directs the conjugate addition to the *β*-position of the ketone.[20] Thus, a plausible mechanism for the reaction is that suggested by Nahm and Weinreb,[21] although here, the chelate dissociation is followed by conjugate addition of HN(OMe)Me on the intermediate acetylenic ketoester to form either product **3** or **4** (Scheme 2).

The structure of α-enaminoketoester **4a** was assigned by HMBC and NOESY magnetic resonance experiments (Supporting Information), showing vinylic proton cross-peaks to one carbon in the olefin and protons on the Me(MeO)N group, respectively. ^{1}H NMR spectral correlations supported the same geometry for the other adducts **4b**−**e**. α-Enaminoketoesters, such as **4a**−**e**, are not easily accessible, and even though this one-step procedure is less regioselective

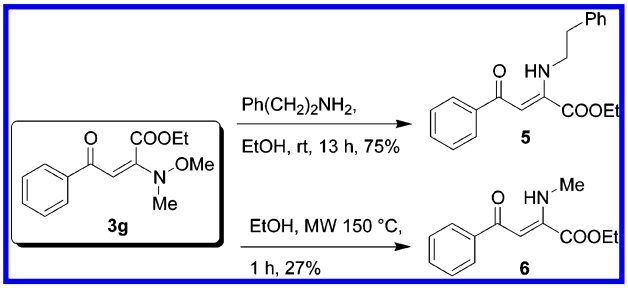
Scheme 2. Mechanistic Proposal for the Reaction of Weinreb Amides with the Sodium Acetylide of Ethyl Propynoate



and therefore provides both regioisomers, it may be advantageous over alternative routes that consist of several reaction steps.[22]

It was found that the Me(MeO)N group in *β*-enaminoketoester **3g** could be exchanged by aminolysis to form *β*-enaminoketoester **5** in high yield (Scheme 3). After

Scheme 3. Aminolysis and Reduction of **3g**



establishing the reactivity of *β*-enaminoketoester **3g**, the cyclocondensation of *β*-enaminoketoesters **3a**, **3d**, **3g**, and **3k** with hydrazine derivatives was investigated. Initially, the reaction was performed by conventional heating in abs. EtOH as previously reported.[9] However, in EtOH, a byproduct was observed during the optimization process when the reaction mixture was heated by microwave irradiation. Subsequently, heating of *β*-enaminoketoester **3g** by microwaves at 150 °C in abs. EtOH afforded *β*-enaminoketoester **6** (Scheme 3), which is similar to **3g** but stabilized by intramolecular hydrogen bonding and therefore is a less suitable reactant in cyclocondensations. A solvent capable of suppressing the reduction (e.g., chloroform)[23] was considered since it was

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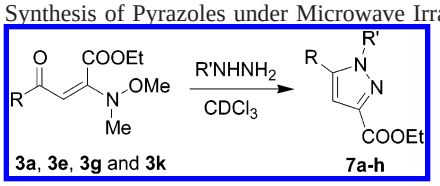
speculated that this might funnel the reaction pathway back into the cyclocondensation manifold. Indeed, in most cases, heating in deuterated chloroform gave pyrazoles **7a**−**h** (Table 2, entries 1−8) in yields that were considerably higher than those from conventional heating in abs. EtOH. The observed regioselectivity was exceptional: none of the other regioisomers were detected. Previously, Schmidt et al.[9] reported that α,γ-diketoesters give low regioselectivity, whereas Veronese et al.[24] reported that β-enaminoketoesters having an unsubstituted amino group give high regioselectivity.

Table 2. Synthesis of Pyrazoles under Microwave Irradiation[a]



entry	R	R′	time (h)	yield (%)[b]
1	Me	Me (**7a**)	2 (1+1)	42
2		Ph (**7b**)	2 (1+1)	72
3	$Ph(CH_2)_2$	Me (**7c**)	1	59
4		Ph (**7d**)	1	54
5	Ph	Me (**7e**)	1	85
6		Ph (**7f**)	2 (1+1)	94
7	$2,4\text{-}Cl_2C_6H_3$	Me (**7g**)	1	76
8		Ph (**7h**)	1	67

[a] General method: β-enaminoketoesters (**3a**,**d**,**g**,**k**, 0.030 mmol) and methylhydrazine (0.036 mmol, entries 1, 3, 5, and 7) or phenylhydrazine (0.036 mmol, entries 2, 4, 6, and 8) heated at 100 °C in $CDCl_3$ (0.6 mL) by microwave irradiation. [b] Isolated yields after preparative HPLC.

In conclusion, this report describes the reaction of ethyl propynoate with Weinreb amides, furnishing *N*-methoxy-*N*-methyl-β-enaminoketoesters, such as **3a**−**e**, **3g**−**i**, and **3k**. β-Enaminoketoesters are versatile synthetic precursors, and the alternative procedures reported to date,[27] often from α,γ-diketoesters[28] or acetylenic ketoesters,[20] can be varied by using the protocol presented in this communication, thereby providing additional flexibility to the overall synthesis of heterocycles.

Second, enaminones **3a**, **3d**, **3g**, and **3k** served as synthetic intermediates, undergoing microwave-assisted regioselective cyclocondensations, yielding pyrazoles **7a**−**h**. We are currently exploring alternative routes to other bioactive scaffolds, such as pyridines, pyrimidines, isoxazoles, thiazoles, and pyrroles, employing β-enaminoketoesters as synthetic intermediates.

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Note Added after ASAP Publication. References were inadvertently omitted and highlighted fonts were left in previous pdf version of Supporting Information posted ASAP June 29, 2006; corrected version posted June 29, 2006.

Supporting Information Available: Experimental procedures and spectroscopic data for compounds **2b**−**f**, **2h**−**k**, **3a**−**e**, **3g**−**i**, **3k**, **4a**−**e**, **5**, **6**, and **7a**−**h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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