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Chemoselective Dieckmann-Like Condensations Using N-Methoxy-N-Methylamides

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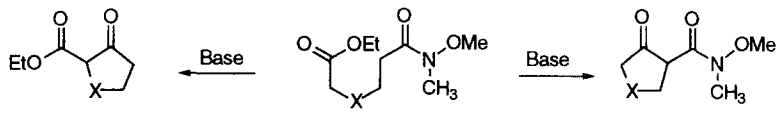
Abstract: The use of N-methoxy-N-methylamide as a chemoselective group in Dieckmann-like condensation is described. The chemoselectivity in these cyclizations is dependent on the counterion of the base employed.

In connection with the total synthesis of hydroxylated indolizidine alkaloid natural products[2] we required ready access to large quantities of N-protected-3-ketoproline esters. Dieckmann condensation[3] has been the basic methodology for the preparation of alicyclic and heterocyclic β-keto esters. However, reactions of unsymmetrical diesters are often problematic because of the formation of regioisomeric products.[4] Dieckmann condensations can be carried out under mild conditions using dithiol diesters[5] and with good regiocontrol using half-thio diesters.[6] Dieckmann cyclizations have also been employed for the preparation of β-ketoamides with limited success, the reaction being most useful for the preparation of secondary amides.[7]

The manipulation of N-methoxy-N-methylamides[8] as a carbonyl equivalent has found wide synthetic applications.[9] Turner and Jacks[10] have shown that ester enolates react cleanly with Weinreb amides to produce β-keto esters in moderate to good yields. Our goal was to explore the ability of the N-methoxy-N-methylamide to function as a chemoselective group in Dieckmann-like condensations (Scheme 1). The success of the Weinreb amides as a carbonyl synthon can be attributed to the formation of a stable chelated intermediate after nucleophilic addition. We surmised that one may obtain selectivity in Dieckmann condensations using half-Weinreb amide esters by modulating the stability of the intermediate chelate with variation in reaction conditions and the nature of the counterion. We present here the realization of the above hypothesis and illustrate an alternative strategy for a chemoselective Dieckmann condensation wherein β-ketoamides[11] (**2** → **3**) or β-ketoesters[12] (**2** → **1**) can be prepared selectively.

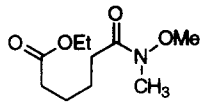
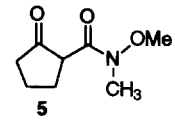
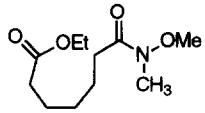
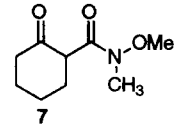
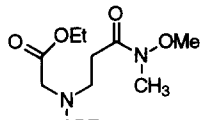
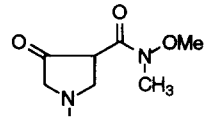
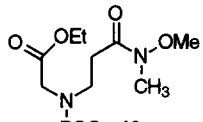
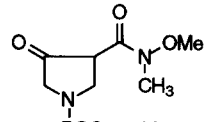
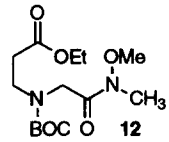
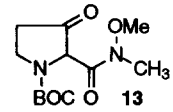
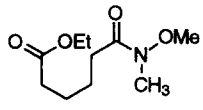
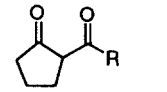
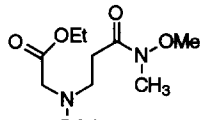
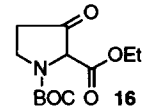
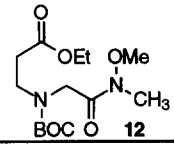
Scheme 1



1 **2** X = CH_2, NR **3**

The preparation of the appropriate Dieckmann substrate was accomplished by two different procedures. Substrates from glutaric and adipic acid (**4** and **6**) were prepared in high yields by treatment of the corresponding half ester acid chlorides with N,O-dimethyl hydroxylamine in the presence of pyridine.[13] The unsymmetrical amide esters (**8**, **10**, and **12**, Table) for ketoproline synthesis were prepared by a three step sequence. Substrate **8** and **10** were obtained by alkylation of ethyl glycinate with N,O-dimethyl-3-bromopro-

Table. Chemoselectivity in Dieckmann-Like Condensations

Entry	Starting Material	Base	Reaction Conditions	Product	Yield, %[a]
1	 **4**	KOt-Bu (2.5 eq)[c] NaOt-Bu (2.5 eq)[c] LiOt-Bu (2.5 eq)[c]	0 °C, 10 min, Toluene same as above same as above	 **5**	72 <1 <1
2	 **6**	KOt-Bu (2 eq)[c]	0 °C, 30 min, Toluene	 **7**	87
3	 **CBZ 8**	KOt-Bu (2.5 eq)[c]	0 °C, 10 min, Toluene	 **CBZ 9**	81
4	 **BOC 10**	KOt-Bu (2.5 eq)[c]	0 °C, 30 min, Toluene	 **BOC 11**	82
5	 **BOC O 12**	KOt-Bu (2.5 eq)[c] KHMDS (1.2 eq)[d]	0 °C, 30 min, Toluene 0 °C, 30 min, Toluene	 **BOC O 13**	72 78
6	 **4**	$BrMgNEt_2$ (1.2 eq)[d] LHMDS (1.2 eq)[d] KHMDS (1.2 eq)[d]	0 °C to rt, 6 h, THF -78 °C, 2 h, THF 0 °C, 10 min, Toluene	 **R = OEt 14** **R = N(Me)OMe 15**	20[b] **14:15** = 1:3.3 74[b] **14:15** = 2.3:1 74[b] **14:15** = 1:99
7	 **BOC 10**	LHMDS (1.2 eq)[d] LDA (1.2 eq)[d]	-78 °C, 2 h, THF -78 °C, 2 h, THF	 **BOC O 16**	73
8	 **BOC O 12**	LDA (1.2 eq)[d] LHMDS (1.2 eq)[d] KHMDS (1.2 eq)[d]	-78 °C, 4 h, THF -78 °C, 2 h, THF -78 °C, 2 h, Toluene	Starting Material Starting Material Starting Material	

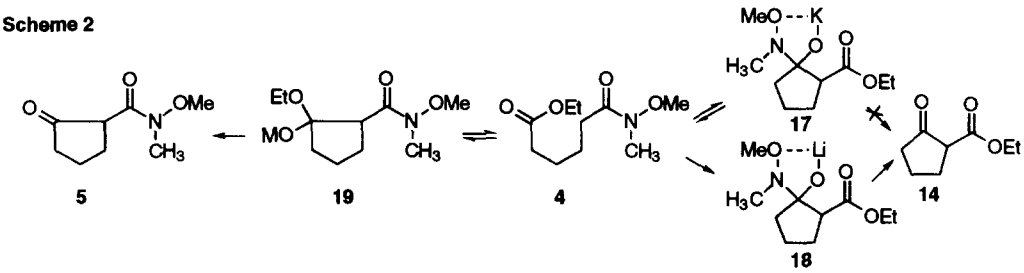
[a]Yields are for column purified materials. [b]Ratios were determined from NMR and/or GC integration. [c] KO-t-Bu was added to a solution of the substrate. [d]Substrate was added to a solution of the amide base.

panamide[14] followed by N-protection with either CBZ-Cl or $(Boc_2)O$. Similarly, alkylation of β-alanine ethyl ester hydrochloride with N,O-dimethyl-2-chloroacetamide[15] followed by N-protection furnished substrate **12**.

The initial cyclization experiments focused on the preparation of the β-ketoamides. Treatment of the half-amide ester **4** with KO*t*-Bu (Rapoport's[4a] conditions) in toluene as the solvent and optimization of the reaction parameters (time, equivalents of the base, and temperature) gave **5** as the sole product (see Table). Use of other bases (NaO*t*-Bu or LiO*t*-Bu) gave only traces of the desired ketoamide. The best reaction conditions for the formation of ketoamides **5** are 2-2.5 equivalents of KO*t*-Bu, 0 °C, and short reaction time. Use of less than 2 equivalents of the base furnished lower yields of the desired product. Under these optimized conditions, the ketoamides (**5**, **7**, **9**, **11**, and **13**) were obtained as a single regioisomer in high yields (72-87%) (entries 1-5, table). The selective formation of β-ketoeters from the half-ester amides required the use of lithium amide bases. Thus, treatment of **4** with 1.2 equivalents of either LDA or LHMDS in THF at -78 °C for 2 h followed by quenching at the same temperature led to a mixture of the keto ester and the ketoamide in good combined yields (entry 6) with moderate preference for the former. The selectivity of this reaction could not be improved on with changes in solvent, time, temperature, or the nature of the counter ion. On the other hand, treatment of **10** with LDA or LHMDS produced the β-ketoester **16** exclusively (entry 7). A similar reaction with **12** gave only traces of the desired product.

The chemoselectivity in the above reactions are dependent on the base employed and a mechanistic rationale is shown in Scheme 2. Reaction of **4** with KO*t*-Bu results in equilibrium deprotonation either α- to the ester or amide.[16] Deprotonation α- to the ester followed by nucleophilic attack at the amide produces **17**. Intermediate **17**, a potassium alkoxide with limited chelation stability and a poor amide leaving group, reverts to **4**. Deprotonation α- to the amide followed by nucleophilic attack at the ester furnishes **19** (M = K) which undergoes elimination of ethoxide to give **5** (an irreversible process due to further deprotonation of the β-ketoamide). Thus, reactions using KO*t*-Bu as the base produces the β-ketoesters as the sole product.

Scheme 2



Cyclizations using lithium amide bases follow a different path. Deprotonation α- to the ester followed by nucleophilic attack at the amide produces **18**, a stable lithium chelate, which provides **14** after workup. Similarly, **4** gives **5** with attack of the lithium enolate at the ester carbonyl. The product distribution in this experiment (entry 6) is dependent on the kinetic acidities at the two different α-sites. The keto ester product being formed preferentially, reflecting the higher acidity α- to the ester. The effect of kinetic acidity on the mode of cyclization is further demonstrated by entry 7, wherein the doubly activated proton α- to the ester is deprotonated, furnishing **16** as the sole product. The non reactivity of **12** remains unexplained at this time.

In conclusion, we have shown that N-methoxy-N-methylamide is an effective chemoselective group in Dieckmann-like condensations. The cyclizations proceed with good selectivity depending on the base. Application of this novel cyclization in synthesis of natural products is underway.

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1. Undergraduate Research Participant.

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13. All new compounds prepared showed physical, spectral (IR, NMR, and MS), and analytical data consistent with their structure.

14. Prepared from 3-bromopropinoyl chloride and N,O-dimethylhydroxylamine.

15. Prepared from 2-chloroacetyl chloride and N,O-dimethylhydroxylamine.

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