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AMIDOACETONE ENOLATE ANIONS: ALKYLATION AND MICHAEL REACTION

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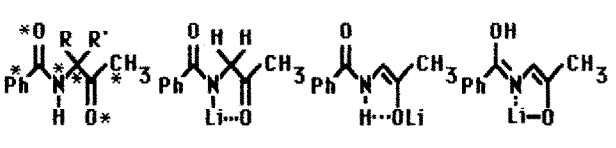
Summary: The lithium enolate derived from benzamidoacetone (**1**) can be regiospecifically alkylated at C(1) and stereospecifically added in conjugate fashion to cyclohexenone without resorting to protection of the free NH. Comparison is made with alkylations of methyl hippurate.

Several years ago Gerst and coworkers reported[1] the enolate anion generation and subsequent trimethylsilylenol ether formation from an extensive series of α-aminoketones. Under kinetic conditions most of these substrates, all of which contained fully substituted α-nitrogen atoms, gave regioisomeric mixtures of enolates ranging from 5:1 to 1:1. We are interested in the potential use of the enolates of aminoacetone derivatives, including those which still contain an NH (i.e., $WHNCH_2COCH_3$), in carbon-carbon bond forming reactions and have therefore carried out the studies described here.

Benzamidoacetone (**1**)[2] (from $H_2NCH_2CHOHCH_3$ + PhCOCl then Jones oxidation), which upon deprotonation contains six potential sites (*) for alkylation, gave only the carbon-methylated product, 3-benzamidobutanone (**2a**),[3] when converted to its

	R	R'
1	H	H
2a	Me	H
2b	Bzl	H
2c	nBu	H
3a	Me	Me
3b	Bzl	Bzl
3c	nBu	nBu

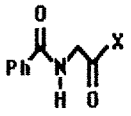


4 **5** **6**

monoanion by exposure to one equivalent of LDA, LiHMDS, or KH and then CH_3I in THF (-78°C to 0°C; with or without HMPA; ~60% yield[4]). Moreover, subsequent treatment of **2a** with LDA (1 eq) and CH_3I gave the geminally methylated adduct **3a**[2] as the only alkylated product. We presume that the amide NH in **1** (or **2a**) is kinetically removed to generate the amide anion **4** and that

subsequent proton transfer(s) generate(s) the thermodynamically favored,[5] dipole-stabilized,[6] ketone enolate anion **5** or the tautomeric and delocalized anion **6**.[7] This lithio anion can also be alkylated by $PhCH_2Br$ (-78°C) and nBuI (-78 to 0°C; nBuBr was much slower) to give **2b**[2] and **2c**[2] in 42 and 35% respectively. Competitive, geminal bisalkylation to generate **3b**[2] and **3c**[2] was a problem in these cases, but could be minimized by use of the lowest possible temperature at which the alkylation rate was convenient.

Relevant to these observations are the results of Krapcho and Dundulis[8] who described the alkylations of the *dianion* derived from the benzamidoester, ethyl hippurate (**7**), and of the *trianion* from hippuric acid (**8**) (generated with two and three equivalents of LDA respectively). Both substrates gave only the products of C-alkylation. In order to probe whether a carboalkoxy group might sufficiently destabilize (relative to the ketone group present in **1**) the enolate anion **9** to tip the thermodynamics in

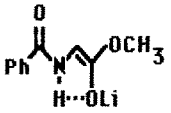


X

7 OEt

8 OH

11 OMe



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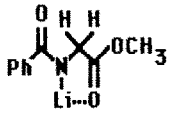

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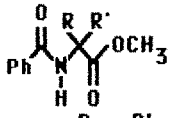


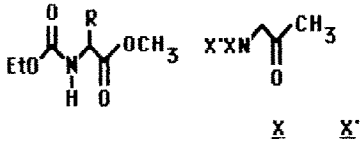
	R	R'
12a	Me	H
12b	Bzl	H
12c	nBu	H
13a	Me	Me
13b	Bzl	Bzl
13c	nBu	nBu
13d	Me	Bzl

favor of the amide anion **10**, we studied the generation and alkylation of the *monoanion* accessible by exposure of methyl hippurate (**11**) to one equivalent of LDA. Once again substitution occurred exclusively on the α-carbon when the anion was exposed to CH_3I, $PhCH_2Br$, or nBuBr (all at -78°C with warming to 0°C for 15 min) to generate the monoalkylated esters **12a**, **12b**, and **12c**[2] in yields of 52 - 61%. Small amounts of the bisalkylated products **13a-c** and unreacted methyl hippurate were often observed. It was possible to introduce two different geminal substituents; deprotonation of N-benzoyl methyl phenylalanate (**12b**) with LDA (1.5eq) and methylation gave **13d**[2] in 48% yield.

Under the hypothesis that dipole stabilization of enolates **5** and **10** would be reduced by replacement of the benzamide by a carbamate moiety, the N-ethoxycarbonyl derivative of methyl glycinate (**14**) was treated with LDA (1.2 eq) and methyl iodide. Once again the only alkylated product was the carbon-substituted, alanine derivative **15**.

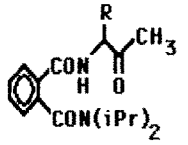
In the ketone series the effect of replacement of the amide NH by an alkyl or carbonyl carbon was probed by studying the anions derived from N-methyl benzamidoacetone (**16**,[2] from PhCONHMe, KH, $CH_3(=CH_2)CH_2Cl$, NaI (cat), THF, Δ; then $NaIO_4$, OsO_4 (cat), THF/H_2O; 82% overall), N,N-biscarboethoxy aminoacetone (**17**),[2] and phthalimidoacetone (**18**)[1] (in the last case it was necessary to use $LiN(TMS)_2$ as the base since the more nucleophilic LDA led to isolation of major amounts of the N,N-diisopropyl-

amides **19** and **20** after methylation). In all three instances the site of anion formation was verified as the nitrogen-bearing carbon by efficient trapping as the enolbenzoates **21a**,[2] **21b**,[2] and **21c** (PhCOCl, -78°C, single stereoisomer of undetermined geometry). Thus, the presence of an NH is not mandatory for regiocontrol in the anion generation. However, all of these substrates

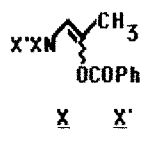


	R
14	H
15	Me

	X	X'
16	PhCO	CH_3
17	EtO_2C	EtO_2C
18	-Phth-	



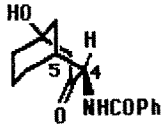
	R
19	H
20	Me



	X	X'
21a	Me	COPh
21b	EtO_2C	EtO_2C
21c	-Phth-	

bear at least one carbonyl-containing substituent on the nitrogen which may be responsible for directing the base/metal ion pair to the more hindered α-protons. All of these more substituted anions, as their lithio salts, were much less reactive toward methyliodide than the NH-containing analogs discussed above. Deprotonation of **16** or **17** followed by exposure to excess CH_3I at 60°C in THF resulted only in the recovery of starting material. The lithio anion from **18** was partially methylated after 17 h at 60°C in the presence of HMPA and the potassium salt of **16** also gave some methylation product along with recovered **16**.

We are also interested in the Michael addition of α-aminoketone enolate ions. The anion **5/6** adds to cyclohexenone (-78°C to RT) in a tandem Michael/aldol process to generate the crystalline adduct **22**[2] (~50%). The same product, whose stereochemistry was deduced by ^{1}HNMR decoupling and difference NOE techniques, was also generated in 62% yield when **1** and cyclohexenone were coexposed to a *catalytic* amount of NaH in THF at 25°C. We do not know whether the observed stereospecificity is the result of kinetic or thermodynamic control.



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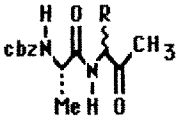
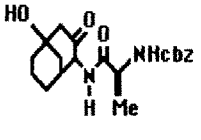


	R
23	H
24	Me



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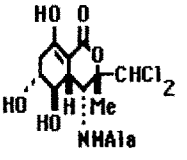

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Finally, initial experiments using Z-alaninamidoacetone (**23**,[2] from DCC/HOBT coupling of $H_2NCH_2CH(OH)CH_3$ with Z-Ala-OH (83%) followed by PCC oxidation (46%)) have demonstrated that molecule's propensity toward formation of analogous methylation (LDA, CH_3I to give **24** as a ~1:1 diastereomeric mixture) and Michael/aldol (cat NaH, cyclohexenone to give **25**) products, although only in low yield thus far. We are continuing to pursue this chemistry and its possible application in a synthesis of bactobolin (**26**).[9] It is significant that the stereorelationship between C(4)-C(5) in **22** and in **26** are the same.

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References and Notes:

1 Garst, M. E.; Bonifiglio, J. N.; Gruddoski, D. A.; Marks, J. Tetrahedron Lett. 1978 2671 and J. Org. Chem. 1980, **45**, 2307.

2 This material gave a satisfactory combustion analysis as well as ^{1}HNMR and IR data in full accord with the assigned structure.

3 Steglich, W.; Hofle, G. Chem. Ber. 1969, **102**, 883.

4 Yields refer to material after purification by MPLC on SiO_2.

5 It is not unreasonable that a species like **5** should be more stable than the secondary amide anion **4** if one considers that the pKa's of CH_3COCH_3 (26.5) and H_2NCOCH_3 (25.5) in DMSO differ by only one unit: Bordwell, F. G.; Algrim, D. J. J. Org. Chem. 1976, **41**, 2507.

6 Beak, P.; Reitz, D. B. Chem. Rev. 1978, **78**, 275.

7 The possibility off the enolate anion being less stable but kinetically more reactivce than the amide anion cannot be excluded.

8 Krapcho, A. P.; Dundulis, E. A. Tetrahedron Lett. 1976, 2205.

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