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The Effect of Base and Additive on the Alkylation of Methyl Hippurate.

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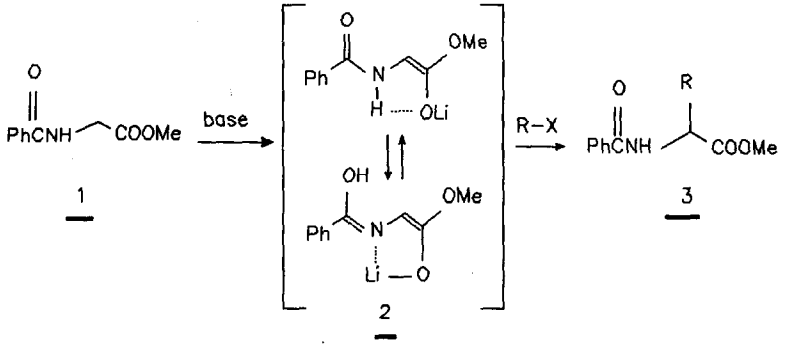
Abstract: *Contrary to a published report, C-alkylation of methyl hippurate requires two equivalents of base. The choice of additive (TMEDA or HMPA) influences the result. Deuteration of the enolate gives results which depend on both the deuterium source and the nature of the additive.*

C-alkylation of derivatized glycine ester enolates is an attractive approach to the preparation of higher amino acids.[1] We[2] and others[3] have investigated the reaction using imines as the N-protecting group and some cyclic N-acylated derivatives have also been examined.[4] As an extension of our work on camphor imines[2], we decided to examine the more complex acyclic N-acyl systems.

In 1976, Krapcho reported[5] that the (red) trianion of hippuric acid could be generated using 3 equiv. of LDA and 3 equiv of TMEDA as evidenced by 80% C-deuteration using D_2O. This trianion gave 40-60% isolated yields of mono-C-alkylated products. In the absence of TMEDA no alkylation took place. The use of alkyllithium bases and TMEDA gave lower yields of alkylated products. It was also noted that methyl hippurate (1) could be C-alkylated in modest and variable yield using 2 equiv. of LDA and 2 equiv. of TMEDA. The putative dianion was generated as a thick yellow suspension in THF and alkylated as such.

In 1985, Hoye reported[6] that methyl hippurate (1) could be C-alkylated using ONE equiv. of LDA and one equiv of HMPA. This result is unexpected in view of the kinetic acidity of the amide N-H bond. A complex series of equilibria leading to the formation of 2 were proposed to account for this result (Scheme 1) . The data suggested that the nature of the additive may be crucial to successful alkylation. Further, the method of generation of the LDA used by Hoye appeared to differ substantially from that used by others in that HMPA was present during the addition of the BuLi to the diisopropylamine (DIPA) solution.

Scheme 1.



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It should be expected that stereochemical, and perhaps chemical results of the alkylation of chiral glycine derivatives of this type will be affected by the physical state (mono- vs. dianionic, degree of aggregation, etc.) of the enolate, but in spite of the interest in glycine alkylation, only one oblique reference to this report has appeared in the literature in the intervening 6 years.[7] Very recently, a similar report on the alkylation of α-acylamino ketones has appeared.[8]

Seebach[7,9] has provided much information on the effects that lithium salts can have on the chemical and physical properties of enolates, particularly those derived from amino acid constituents of peptides. Significant changes in solubilities or formation of "mixed aggregates" may drastically affect their reactions. Other workers[10] have noted unusual effects caused by the presence of Li cations. In Seebach's work, all amino acid residues were present both as their carboxyamides and N-acyl derivatives. There were no ester functions present and the stereochemistry associated with amide enolates has been shown to drastically reduce the rate of deprotonation of α-substituted amino acids.[7] Nevertheless, the yields have shown a remarkable dependence on the presence of excess Li cations in the reaction mixture. Before examining the stereochemical questions, it was necessary to clarify and confirm what was necessary to achieve good chemical yields fot the N-acyl aminoesters. To this end, we have examined a series of alkylations and deuterations of methyl hippurate (1) under a number of different reaction conditions designed to elucidate the importance of the nature and number of equivalents of additive (HMPA, TMEDA etc.) and base.

Two steps are involved in the alkylation process. The reaction of base with 1 must lead to an enolate. The chemical reactivity of this enolate which will determine the success or failure of alkylation depends, at least in part, on its aggregation state, degree of complexation and ionic nature. Historically, deuteration and alkylation have been used as probes to examine these two steps. While the absence of deuterium incorporation is not a reliable indicator of the absence of an enolate, when LDA is used as the base[11], the incorporation of deuterium is usually taken to indicate the presence of enolate and we decided to examine both the deuteration and alkylation of the species generated by the treatment of methyl hippurate with varying numbers of equivalents of LDA which had been generated in a variety of ways to further substantiate or refute Hoye's results. The attempts to monitor the formation of the enolate by deuteration experiments are outlined in Table 1.

The deuterium incorporation observed using MeOH-d_4 appears to indicate that essentially complete enolate formation is occurring when 2 or more equivalents of LDA are used, but with either D_2O or HOAc a similar conclusion cannot be reached. However, the fact that significant exchange of ester CH_3 for CD_3 is seen implicates the involvement of methoxide and it may be that the higher levels of deuterium incorporation result from the presence of LiOMe in the reaction mixture and do not necessarily indicate the presence of the enolate. [It is interesting to note that the use of MeOD in place of MeOH-d_4 would not have revealed this important point.] Casting some doubt on this is the fact that quenching the reaction carried out with one equiv. of LDA with MeOH-d_4, conditions which would also generate methoxide, afforded very little C-deuteration. What is clear is that the method of formation of the LDA contributes to the deuteration result. Under otherwise identical conditions, and using the same deuterium source, the use of LDA generated in the presence of 1 equiv. of HMPA (Hoye's method) gives significantly less deuterium incorporation than the use of LDA to which the HMPA is added subsequently. When the number of equivalents of LDA is 2 or greater, even MeOH-d_4 gives excellent incorporation only if the HMPA is introduced after the LDA is formed. This may

simply reflect a lower rate of deuterium exchange caused by methoxide, but the effect is unexpected.

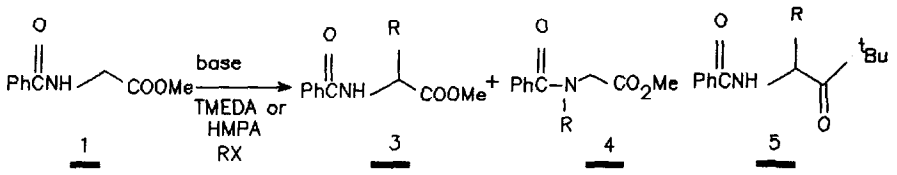
TABLE 1
DEUTERATION OF METHYL HIPPURATE

Equiv LDA[a]	deuterium source	% CH_2 -->CHD[b,c] Equiv HMPA 0	1	2	3
1[d]	HOAc-d_4	0			
	D_2O		0		
	MeOH-d_4	25	<5		
2[d]	HOAc-d4	0	0	<5	
	D_2O		8	<20	
	MeOH-d_4	60	100	100	
2[e]	HOAc-d_4		0	4	
	D_2O		5		
	MeOH-d_4		66	30	
3[d]	HOAc-d_4				0
	D_2O				100
	MeOH-d_4				100
3[e]	HOAc-d_4				0
	D_2O				50
	MeOH-d_4				40

[a] The enolate formed with 1 equiv was a light yellow, clear solution, that formed from 2 equiv was a yellow semi-solid and that formed using 3 equiv was a deep red-brown solution; [b] NMR integration data, ± 10%; [c] In all cases using MeOH-d_4, significant transesterification to give CD_3 incorporation was observed by ^1H NMR. Significant N-deuteration was not observed due to aqueous work-up; [d] Method A in experimental; [e] Method C in experimental (Hoye's Method);

The results of the alkylation of the "enolate" generated in a number of ways are shown in Table

Scheme 2



2. In the presence of either HMPA or TMEDA and using ONE equivalent of LDA, no significant C-alkylation could be observed, regardless of the method of generation of the LDA. This is in direct contrast to the results reported by Hoye[6], but is not surprising in light of the deuteration results shown in Table 1. Some N-alkylation did take place when HMPA was the additive. The amount of starting material remaining after reaction was dependent on the number of equivalents of HMPA used but, in every case, only traces of C-alkylated products were formed. The use of DMPU[12] or the presence of LiCl in the reaction mixture did not lead to any reaction.

TABLE 2
REACTIONS OF METHYL HIPPURATE USING LDA

Run	Equiv of base	Method[a]	additive (equiv)	Halide	Yield of Alkylation[b] C	N
1	1	A	TMEDA (1)	BnBr	0	0
2	1	A	TMEDA (3)	BnBr	0	0
3	1	A	TMEDA (1)	MeI	0	0
4	1	A	HMPA (1)	BnBr	<5	25
5	1	B	HMPA (1)	BnBr	<5	25
6	1	C	HMPA (1)	BnBr	<5	25
7	1	A	HMPA (1)	MeI	<5	30
8	1	A	HMPA (3)	BnBr	<10[c]	50
9	1	A	HMPA (3)	MeI	<10[c]	60
10	1	A	DMPU (1)	BnBr	<5	<5
11	1	D	LiCl (1)	BnBr	0	0
12	2	A	------	MeI	75	0
13	2	A	TMEDA (1)	BnBr	60	0
14	2	A	TMEDA (2)	MeI	70	0
15	2	A	HMPA (1)	BnBr	65	0
16	2	A	HMPA (1)	MeI	75	0
17	2	A	HMPA (3)	BnBr	55[c]	<5
18	3	A	------	MeI	60[d]	0

[a] See experimental; [b] ±5%; [c] plus 15% of butyl ester; [d] +20% dimethylated.

In order to avoid the potential difficulties engendered by the association of DIPA with the enolate or the use of excess BuLi alluded to above, the use of ^{t}BuLi was investigated. Two equiv. of this base, in the presence of either TMEDA or HMPA, afforded ketone **5** as the major product. This was the case regardless of the order of addition of the reactants and suggests that, at least in these cases, the formation of the enolate is relatively slow.

Significant amounts of dialkylated products were obtained in run 18 where 3 equivalents of LDA was used. This suggests either that, unlike the case of the peptides[7], the mono-alkylated product is capable of being deprotonated or that doubly deprotonated enolates[13] can be formed. Both are important points if stereochemical questions concerning the alkylation of chiral derivatives are to be addressed. At this time it is not clear if this problem is more severe with one additive or the other. This question will be addressed in the context of reactions of chiral esters.

In the presence of TWO equivalents of LDA, efficient C-alkylation was observed. While the nature of the product seems independent of the additive used, the chemical yield is not. Consistently higher yields were obtained using HMPA as the additive.

In runs 8, 9 and 18, small amounts of the butyl ester corresponding to 1 and its alkylated product and products of both C- and N-alkylation could be seen by HPLC.

The differences between HMPA and TMEDA are interesting. Generally, the two are thought to be interchangeable and the choice between them is based on availability and/or safety considerations. Our results clearly show that this is not always the case. The role usually ascribed to these additives is as a deaggregating agent for the lithium enolate. However, the monodentate vs. bidentate nature of these compounds must be important in controlling the coordination sphere of the metal atom and the reactivity of the enolate. The precise mechanism of this influence is still obscure.

In summary, it appears that alkylation of N-acylglycine ester is best accomplished using 2 equiv. of LDA and HMPA. The yields of the reactions are over 75% under these conditions. N-alkylation can be achieved in up to 60% yield by using only one equivalent of base. Our attention has now turned to a systematic investigation of the stereochemical questions raised by application of this procedure to chiral derivatives of 1. The results of this investigation will be published shortly.

Acknowledgement: The cooperation of Prof. T.R. Hoye in supplying the experimental procedure used in his laboratory contributed greatly to this work and is greatfully acknowledged.

Experimental

Reaction mixtures were analyzed by ^1H NMR and HPLC using UV detection at 214 nm and a 10 cm reverse-phase C-18 column eluting with 2:3 CH_3CN : 0.005% CF_3COOH in H_2O.

Alkylation Methods.

Method A: (Using 1 equiv. of LDA) At -78°C , a solution of diisopropylamine (140 μL, 1 mmol) and 2.5 N BuLi in hexane (400 μL, 1 mmol) in 3 mL of anhydrous THF was prepared. After 10 min, HMPA (174 μL, 1 mmol) was added and then, after 20 min, ester 1 (195 mg, 1 mmol) dissolved in 2 mL of THF was added. After 30 min, the electrophile (BnBr or MeI, 2 equiv) was added and the mixture was stirred at -78°C for 1 hr and then allowed to rise to ambient temperature over 20 min. The reaction was quenched with 2N HCl and extracted with ether. The ether extracts were washed with water, dried and concentrated to a syrup. Reactions with 2 equiv. of LDA were run in an analogous manner.

Method B: As in Method A except that the ester 1 was added to the THF solution of LDA and, after 20 min, HMPA was added.

Method C:[6] Diisopropylamine (1 mmol) and HMPA (1 mmol) were added to 3 mL of anhydrous THF and then cooled to -78°C . After 10 min, 1 mmol of BuLi (2.5N in hexane) was added dropwise. After 20 min at -78°C, a solution of ester 1 (1 mmol) was added. After 30 min, benzyl bromide (2 mmol) was added, the mixture was stirred for 1 h at -78°C warmed to ambient temperature and was worked up as in Method A.

Method D: (presence of LiCl) 1,2-Dichloroethane (79 μL, 1 mmol) was added to 3 mL of dry THF, followed by of 2.66N BuLi in hexane (380 μL, 1 mmol). The resulting solution of LiCl was stirred at ambient temperature for 30 min, cooled to -78°C and the LDA was generated as indicated in Method A.

Deuterium quenches without additives

Diisopropylamine (2.0, 4.0, or 6.0 mole) was added to THF (5 mL) and the resulting solution cooled to -78°C. n-Butyllithium (1.6 M in hexane; 2.0, 4.0, or 6.0 mmole) was added and the mixture stirred for 0.25 h. Compound 1 (380 mg; 2.0 mmole) was added in THF (5 mL) solution. The mixture was stirred at -78°C for 1 h. The electrophile (d_4-AcOH, d_4-MeOH, or D_20; 0.2, 0.3, or 0.4 mL according to the amount of base used)

was added. The cold bath was removed from the reaction vessel. After 0.5 h, saturated aqueous ammonium chloride solution (5 mL) was added. The mixture was poured into more saturated NH_4Cl solution (25 mL) and extracted with chloroform (2 x 30 mL). The combined extracts were dried (Na_2SO_4) and evaporated to give the crude product that was analysed by nmr.

Deuterium quenches with additives

Diisopropylamine (2.0 mmol) was added to THF (6 mL) and the mixture cooled to -78°. n-Butyllithium (2.0 mmol) was added and the resultant mixture stirred for 10 minutes. At this time HMPA (1 mmol) was added and the mixture stirred for an additional 20 minutes when 1 (1 mmol) in THF (4 mL) was added. The reaction was stirred at -78° for 0.5 h when the electrophile (AcOH-d_4, MeOH-d_4, or D_20: 0.4 mL) was added. The cold bath was removed from the reaction vessel. The reaction was poured into 2M hydrochloric acid (10 mL) and extracted with ether (2 x 10 mL). The combined extracts were washed with water (10 mL), dried (MgSO4), and evaporated.

A sample of the deuterated material was purified by column chromatography on silica gel eluting with 3:7 ethyl acetate-hexane, mp: 82°; IR:vmax(KBr) 3260 (NH) and 1730 (C=O)cm^{-1} NMR: $CDCl_3$ 7.8 (2H, m), 7.6-7.4 (3H, m,), 6.75 (1H, br, NH), 4.27 (1H, d, J = 6 Hz, CH), and 3.80 (3H, s, OMe); ^{13}C NMR: 170.6, 167.6, 133.6, 131.8, 128.6, 127.1, 52.4, 41.7 (split by D); MS: m/z = 195 (M+I), 194 (M+) by chemical ionization. Anal. Calcd. ($C_{10}H_{11}NO_3$): C, 62.17; H, 5.74; N,7.25: Found C, 62.07; H, 5.85; N, 7.28.

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