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ABNORMAL ALKYLATION OF N-BENZYLIDENE-α-AMINOESTER ANIONS WITH α-HALOESTERS

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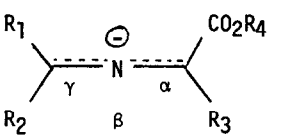
SUMMARY: The title anions, when α-alkyl substituted, alkylate selectively in the γ-position with hindered α-bromoesters. A lower degree of hindrance in either or both reactants tends to favour α-alkylation.

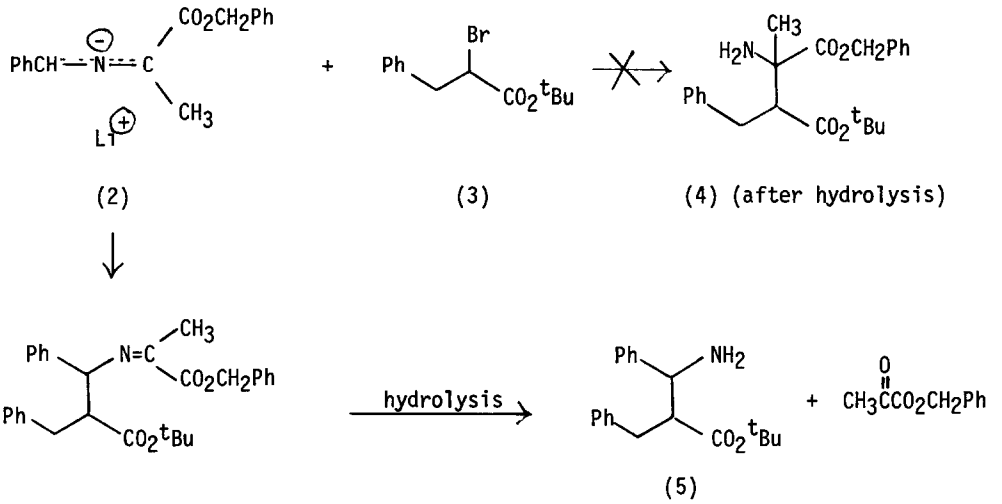
The alkylation of the anion of Schiff bases derived from α-aminoesters has been widely exploited[1] since its development by the Stork group[2] as a convenient route to various α-substituted α-aminoacids. In all reported cases the alkylation of the ambident anion (1) appears to be regiospecific, giving only the α-alkylated product.



(1)

During the synthesis of novel α,α-disubstituted α-aminoacids, we reacted the lithium salt (2) of N-benzylidenealanine benzyl ester with t-butyl 2-bromo-3-phenylpropionate (3) under the usual conditions[2] [-78°, HMPTA-THF, LiN(iPr)$_2$] and hydrolysed the crude product with 1M aqueous citric acid to selectively remove the benzylidene function. Chromatography of the citric acid-soluble basic products gave, to our surprise, none of the desired α-alkylated product (4). Instead, two new amine diastereoisomers were isolated in 22% (m.p. 38-9°) and 14% (m.p. 94-5°) yield. In each case, ^{1}H n.m.r. indicated the absence of the benzyl ester function and the α-methyl group derived from the anion and the presence of two phenyl rings, corresponding to the structure (5).[7] These isomers must result from γ-alkylation in a selective process which is, to the best of our knowledge, unprecedented in this system. From the neutral hydrolysis products, benzyl pyruvate was isolated in 30% yield,[8]

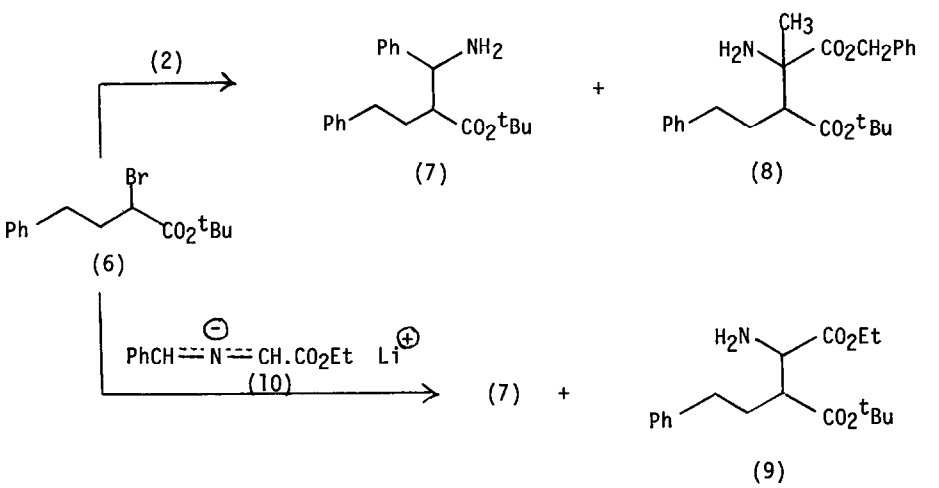
no benzaldehyde being detected. The diastereoisomers (5) were similarly obtained in 58% overall yield using N-benzylidenealanine methyl ester, again with no evidence of α-alkylated products.



(2) (3) (4) (after hydrolysis)

(5)

It is known that alkylation of glycine or alanine-derived Schiff base anions with alkyl bromoacetates gives excellent yields of α-alkylated products.[1a, 2] It seemed that the reversal of regioselectivity observed in our case might be due predominantly to increased hindrance and thus we performed similar reactions using the less hindered homologous bromide (6). Alkylation of (2) with (6) under conditions identical to those described above proceeded in poor yield giving 8% of α-alkylated product (8) and 13% of γ-alkylated product (7). However, the overall reaction efficiency improved when the less hindered glycine anion (10) was alkylated with (6) but in this case the "normal" alkylation predominated, giving 40% of (9) and only 4.5% of "anomalous" α-alkylated material (7).



(7) (8)

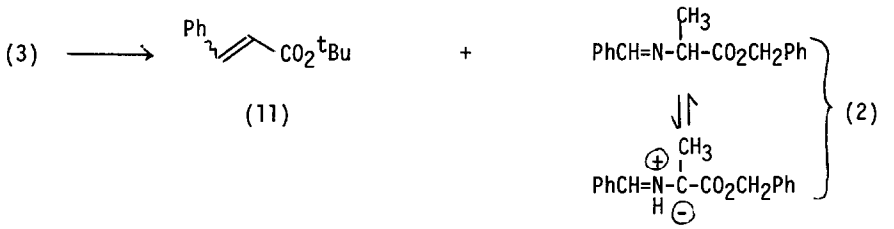
(6)

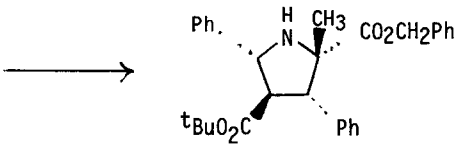
(10)

(7) +

(9)

Further examination of the crude product from (2) and (3) led to the isolation of a minor amine product as a mixture of isomers which equilibrated under chromatography to one crystalline species (m.p. 128-9°). ^{1}H n.m.r. clearly indicated the presence of three phenyl rings. The likelihood that loss of hydrogen bromide from (2) giving t-butyl cinnamate (11) would occur in the basic reaction medium suggested that this product might arise from 1,3-dipolar cycloaddition of (11) to the protonated form of (2) (*i.e.* tautomeric form of the free Schiff base) to give the pyrrolidine (12). This structure was confirmed by m.s. and i.r., the relative stereochemistry and regiochemistry being tentatively assigned on the basis of similar cycloadditions noted by the Merck group[4] and studied in detail by Grigg and co-workers.[5] As would be expected, no cycloaddition by-products were formed in the reactions involving the homologous bromide (6).





(12)

The observed distribution of α- and γ-alkylated products indicates that the reactions of α-haloesters with the anion (1) are particularly sensitive to steric influences, α-alkylation predominating except where the α-positions of both the anion and the halide are crowded, when γ-alkylation occurs with lower efficiency. In this study, other factors known[6] to affect the regioselectivity of allyl anion alkylation, such as the type and degree of solvation of the cation and the hardness of the electrophile are essentially the same. The literature contains few examples of reactions with hindered α-alkylhalides; of those reported,[1a,1b,1c] isopropyl bromide and iodide and 2-bromo- and 2-iodopropane give high (60-95%) yields of α-alkylated products using glycine and alanine-derived anions with no reported γ-alkylation.

We conclude that due caution should be observed in predicting the regioselectivity of α-substituted α-aminoester Schiff base anion alkylation when employing hindered electrophiles.

References and Notes

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7 All new compounds gave 'H n.m.r., i.r. and mass spectra and/or microanalysis (C,H,N) in complete agreement with the assigned structures.

8 Identical (t.l.c., i.r.) with authentic material prepared by uncatalysed esterificati of pyruvic acid.[3]

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