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SELECTIVE MONOPHENYLATION OF AN ACTIVE METHYLENE COMPOUND

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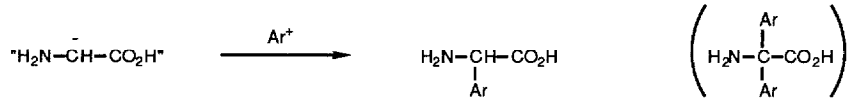
Introduction of an aryl residue into an organic compound is an important synthetic transformation.[1] Our interest in this problem stems from our efforts in the synthesis of monosubstituted α-amino acids from the anionic glycine equivalent **1**,[2] the anion of an active methylene compound.[3] Monoarylation of an active methylene compound such as **1** is of synthetic interest in a general sense because, as detailed below, such a transformation is often difficult, and also because of the particular interest in α-arylsubstituted glycines **2**.[4,5] While the literature is

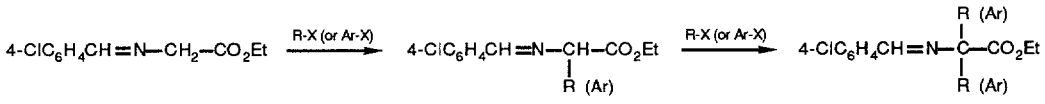


1 **2** **3**

replete with examples of either diarylation of active methylene compounds[6] or monoarylation of active methine compounds,[5,6] there are but few examples of the *selective monoarylation* of active methylene compounds.[7] The problem is to avoid mixtures of starting substrate and mono- and diarylated products since the monoarylated product **2** is normally more acidic than the active methylene starting material (conjugate acid of **1**). Under basic conditions this leads to equilibration of anions, which favors the more stable anion of the monoarylated product, and can lead to subsequent diarylation.[8] Diarylation has often been supressed by using either an excess of base or of the anion of the starting active methylene compound.[7,9] However, the latter situation results in the equally problematic separation of starting material from monoarylated product.

We have reported the acidities of a series of protected amino acid derivatives[10] and the large acid-weakening effect resulting from introduction of an α-alkyl group has been utilized in the *selective monoalkylation* of **7**.[2] It was also noted that, while the arylidene imines of glycine ethyl ester show a normal acid-strengthening effect[11] in going from the active methylene parent **4** to the monophenylated derivative **5b**, the monophenylated derivative in the benzophenone series (**8b**) is 300 times less acidic than its active methylene parent **7**.[10] From

Easy to Dialkylate or Diarylate

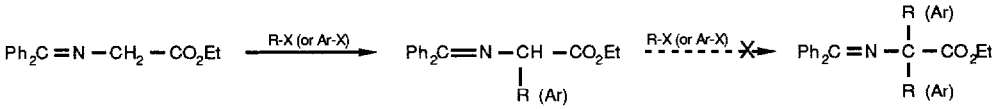


4 (pKa 18.8)

5 a, R=Me (pKa 19.2)
5 b, Ar=Ph (pKa 17.2)

6 a, R=Me
6 b, Ar=Ph

No Dialkylation or Diarylation Observed



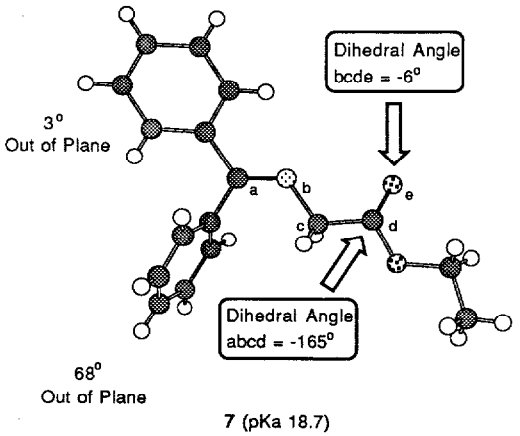
7 (pKa 18.7)

8 a, R=Me (pKa 22.8)
8 b, Ar=Ph (pKa 21.2)

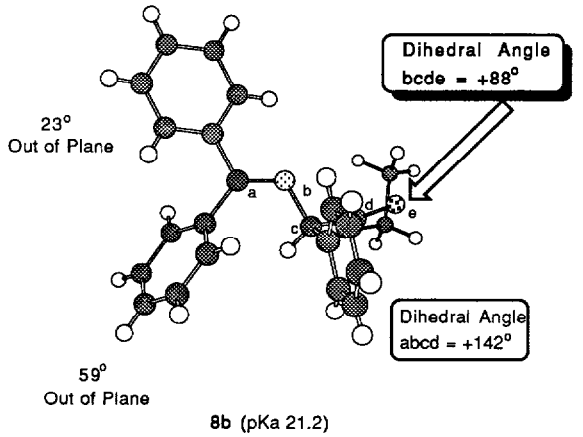
9 a, R=Me
9 b, Ar=Ph
Not Observed

this unusual result, we can anticipate that it should be possible to monoarylate compound **7** without subsequent diarylation being a problem.

The origin of this large decrease in acidity is no doubt steric in nature.[10,11] It was instructive in this regard to examine the crystal structures of the two compounds shown below.[12]



7 (pKa 18.7)

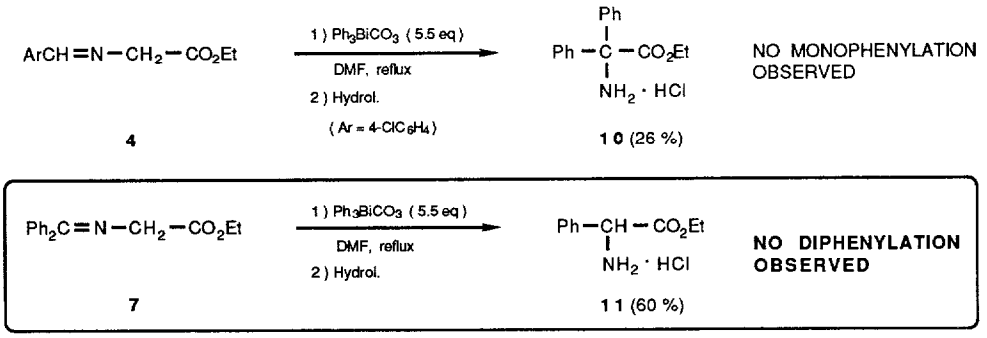


8b (pKa 21.2)

In ketimine **7** the trans phenyl is essentially coplanar with the imino plane (C_a-N_b-C_c in plane of paper) while the cis phenyl is considerably out of planarity. Additionally, the carbonyl group of the ester in **7** is nearly coplanar with the imino plane (6° and 15° out of planarity as indicated by the two dihedral angles shown). In contrast, in the monophenylated product **8b**, both imino phenyls are out of planarity with the imino plane. However, the major conformational difference between **7** and **8b** is that in the latter compound the carbonyl is essentially orthogonal to the plane of the imine bond (88° and 38° dihedral angles). To the extent that these conformational contraints are felt

in the corresponding anions, it would be expected that compound **8b** would be considerably less acidic than its parent **7** since delocalization of negative charge in the anion of **8b** would not be as effective as in the anion of **7**.

The possibility of *controlled arylation of active methylene compounds* based on the knowledge of their acidities has been experimentally realized by phenylation of compounds **4** and **7** with an excess of triphenylbismuth carbonate under neutral conditions[6b,13] followed by hydrolysis of the arylated products to the corresponding amino acid esters. Thus, in the "normal" case of protected glycinate **4**, in which the monophenylated Schiff base ester **5b** is more acidic than starting material **4**, only diphenylated product **10** was isolated. On the other hand, when the benzophenone imine **7** was phenylated and then hydrolyzed, only monophenylated product **11** was obtained. In the latter case, isolated monophenylated Schiff base ester **8b** was identical with an authentic sample prepared independently.[14] Additionally, attempted phenylation of the benzophenone imine of phenylglycine ethyl ester (**8b**) resulted only in recovery of starting material (87%) and benzophenone.



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12. Crystal data for **7**: $C_{17}H_{17}NO_2$, space group $P\bar{1}$, a = 9.976(2), b = 10.212(2), c = 7.545(1) Å, α = 100.42(1), β = 109.29(1), γ = 94.30(1)°; giving D_c = 1.258 g cm^{-3} for Z = 2. A total of 3251 unique intensities were collected. Final residuals were R(F) = 0.0409 and R_w(F) = 0.0453. Crystal data for **8b**: $C_{23}H_{21}NO_2$, space group $P2_12_12_1$, a = 15.547(2), b = 12.897(1), c = 9.006(1) Å; giving D_c = 1.263 g cm^{-3} for Z = 4. A total of 2992 unique intensities were collected. Final residuals were R(F) = 0.0441 and R_w(F) = 0.0453.
13. Preparation of ethyl α-amino-(±)-benzeneacetate hydrochloride (**11**): To an oven dried 100 mL round-bottom flask equipped with a magnetic stirring bar were added ethyl N-(diphenylmethylene)glycinate (**7**)[14] (1.0 g, 3.75 mmol), triphenylbismuth carbonate (3.75 g, 7.5 mmol), and DMF (15 mL). A reflux condenser equipped with a $CaSO_4$ drying tube was attached and the flask was placed in a preheated heating mantle. The mixture was heated at reflux, with stirring, for 20 minutes. The cooled reaction mixture was filtered through Celite and the Celite was washed with diethyl ether (2x25 mL). The filtrate was transferred to a separatory funnel with water (75 mL) and ether (50 mL). The mixture was shaken, the layers were separated and the aqueous layer was extracted further with ether (2x100 mL). The combined ethereal layers were evaporated *in vacuo*, leaving a watery residue. Aqueous HCl (50 mL of 2.0 N solution, 100 mmol) and ether (20 mL) were added and the solution was magnetically stirred at room temperature for 2 hours. The layers were separated; the aqueous layer was washed with ether (3x100 mL) and neutralized with saturated aqueous Na_2CO_3. The aqueous mixture was extracted with ether (2x100 mL); the ethereal extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo* to give crude amino acid ester. The crude product was dissolved in ether (20 mL) and HCl gas was bubbled through the solution for 2-3 minutes. The ether was removed *in vacuo*, the residue was dissolved in acetone (2-3 mL) and ether was added until the solution became cloudy. The resulting white crystals **11** were isolated by filtration: 0.49 g, 60%; mp 201-3° C (lit.[15] mp 200° C).
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