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A SIMPLE, EFFICIENT SYNTHESIS OF β-METHYLENE PHENYLALANINE. A NEW APPROACH TO THE PREPARATION OF β,γ-UNSATURATED α-AMINO ACID ENZYME SUBSTRATE ANALOGS

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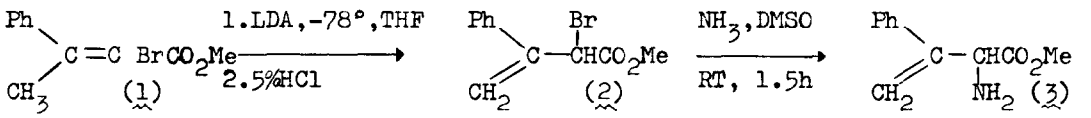
Several synthetic β,γ-unsaturated α-amino acids have recently been developed as specific irreversible inhibitors of pyridoxal phosphate dependent enzymes.[1] A few naturally occurring β,γ-unsaturated amino acids are known to function as specific enzyme inhibitors [2] including rhizobitoxine inhibition of β-cystathionase [3] and 2-amino-4-methoxy trans-3-butenoic acid inhibition of aspartate aminotransferase. [4] In view of this interest in the β,γ-unsaturated α-amino acid structural unit we have sought methods to prepare aromatic derivatives including the presently unknown β-methylene β-aryl α-amino acid system. Such compounds are potential irreversible inhibitors of a variety of pyridoxal phosphate dependent enzymes including aromatic amino acid decarboxylase and aminotransferase enzymes found in animal and bacterial systems. We now report the first synthesis of a β-methylene β-aryl α-amino acid using a straightforward, high yield approach which in the critical step involves simple treatment of an α,β-dibromo ester with ammonia.



We have recently found that a deconjugation reaction employing one equivalent of lithium diisopropylamide in THF solvent at -78°can be carried out on methyl 2-bromo-3-methylcinnamate (1) to give methyl 2-bromo-3-phenyl-3-buteno-

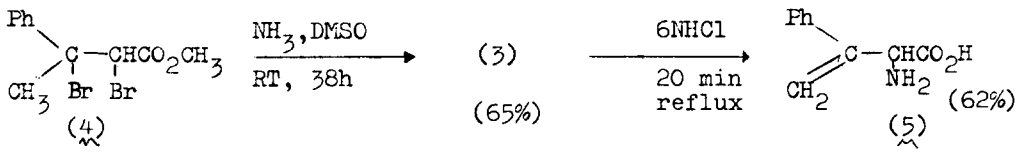
ate (2) in 95% yield apparently without any ill effect due to the presence of the labile bromine substituent. At this point one might envision simple ammonia displacement of bromide in (2) in order to obtain the desired β,γ-unsaturated α-amino acid derivative (3), however, in a closely related case it has been reported that reaction of ethyl 2-bromo-3-butenoate with ammonia gave only low yields of the desired ethyl 2-amino-3-butenoate apparently due to the high relative acidity of the labile α-proton under the conditions employed. [5] However, we have found that treatment of α-bromo ester (2) with saturated ammonia in DMSO at room temperature for 1.5h gave an 88% yield of the desired α-amino ester, namely methyl 2-amino-3-phenyl-3-butenoate (3) thus suggesting that the reaction of ammonia with α-bromo β,γ-unsaturated esters is potentially a very useful approach for the synthesis of the corresponding α-amino β,γ-unsaturated ester system. Secondary amine by-products were not found in any significant amounts in the ammonia-DMSO displacement reactions reported here.

It has been reported [7] that ethyl α-bromo-β,β-dimethylacrylate reacts with piperidine in ethanol to give a mixture of ethyl 2-piperidino-3-methyl-3-butenoate and ethyl 2-piperidino-3-methyl-2-butenoate. This result would suggest that a similar reaction may be possible with ammonia thus allowing for a more direct preparation of simple α-amino β,γ-unsaturated esters. In fact the reaction of methyl 2-bromo-3-methylcinnamate (1) with ammonia in DMSO at room temperature for 24 h leads to an 80% yield of methyl 2-amino-3-phenyl-3-butenoate (3). The α-bromocinnamate (1) can be prepared by base (ammonia [8]) induced dehydrohalogenation of methyl 2,3-dibromo-3-methylhydrocinnamate (4) and thus it is possible to carry out a one pot conversion of (4) to (3) in 65% isolated yield using an excess (saturated solution) of ammonia in DMSO for 38 h at room temperature.

The use of DMSO as solvent is critical to the success of this reaction. Thus for example mainly starting material was left and less than 5% of (3) was formed when (1) was kept in the presence of saturated ammonia in ethanol over a 5 day period. Other solvents such as THF, benzene and methanol were also not useful, however, a low yield was obtained when DMF was employed as the solvent.

The synthesis of β-methylenephenylalanine (5) is completed by acid hydrolysis

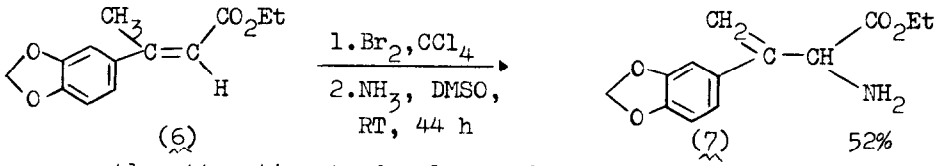
of (3) in 62% isolated yield using refluxing 6NHCl for 20 min, followed by ion exchange chromatography on Dowex 50WX4 cation resin (acid cycle) eluting with water followed by 1MNH_4OH. Evaporation of the ammonia solution gave (5) as a white solid: mp 173-174° (dec) (from methanol); NMR (D_2O): δ 7.33 (s, 5H), 5.53 (s, 1H), 5.43 (s, 1H), 4.60 (s partially obscurred by the HDO peak); ir (KBr): 3200-2600, 1600, 920 cm^{-1}. Anal calcd for $C_{10}H_{11}O_2N$: C, 67.79; H, 6.21; N, 7.91. Found: C, 67.75; H, 6.02; N, 7.78.



The mechanism of conversion of methyl 2-bromo-3-methylcinnamate (1) to methyl 2-amino-3-phenyl-3-butenoate (3) in ammonia DMSO appears to involve initial base induced isomerization to methyl 2-bromo-3-phenyl-3-butenoate (2) followed by ammonia displacement of bromide. This is supported by the result that high yield conversion of the proposed β,γ-unsaturated ester intermediate (2) into the product (3) takes place under the conditions of the reaction (DMSO, 25°) in a relatively short period of time (1.5h) while conversion of α,β-unsaturated ester (1) into (3) requires 24h at 25° in DMSO. This mechanistic interpretation would mean that the proton tautomerization step is the slow step in the overall process. Recently it has been reported [9] that ethyl 2-bromo-3-methylcinnamate reacts with sodium ethanethiolate (0.15 equivalents) to give a low yield (10%) of ethyl 2-bromo-3-phenyl-3-butenoate along with 7% ethyl 2-ethylthio-3-methylcinnamate. These workers also proposed that the deconjugating proton tautomerization step was the slow step in the formation of 2-ethylthio-3-methyl-cinnamate. [10]

We have used this method in the synthesis of other β-methylene α-amino esters Dropwise addition of bromine (0.013 mole) in CCl_4 (40 ml) to a solution of ethyl 3,4-methylenedioxy-β-methylcinnamate (6) [11] in CCl_4 (35 ml) was carried out while the temperature was maintained at -10°. Following the addition the temperature was kept at -5° for an additional 5 min prior to removal of the solvent under reduced pressure. The resulting oil was a mixture of erythro and threo dibromide

isomers. Anhydrous DMSO (65 ml) saturated with ammonia was cooled and added to the crude dibromo ester in a pressure bottle and the solution was allowed to stir for 44h at room temperature. The reaction mixture was then poured into ice cold water and extracted with CH_2Cl_2. Work up using an acid-base extraction procedure gave essentially pure β-methylene amino ester (7)(1.66g, 52% overall yield): NMR ($CDCl_3$,TMS):δ 6.88-6.62 (m,3H), 5.80 (s,2H), 5.20 (s,1H), 5.13 (s,1H), 4.31 (s,1H), 4.03 (q,2H,J=7Hz), 2.08-1.59 (broad singlet,2H), 1.07 (t,3H,J=7Hz); ir (neat): 3380, 3320, 1730 cm^{-1}. An analytical sample was obtained for the hydrochloride salt (from ethanol): mp 164-165° (dec.). Anal calcd for $C_{13}H_{16}NO_4Cl$: C, 54.65; H, 5.65; N, 4.90; Cl, 12,41; Found: C, 54.69; H, 5.57; N, 4.85; Cl, 12.60.



(6) (7) 52%

We are presently attempting to develop methods for cleavage of blocking groups associated with various aromatic amino acid derivatives of medicinal interest. Such methods need to be sufficiently mild to avoid removal of the acidic α proton or destruction of the β,γ double bond. In any case the ammonia-DMSO induced elimination-substitution process reported here appears to be highly effective in generating this labile β,γ-unsaturated α-amino ester system.

References and Notes

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4. R.R.Rando, N.Relyea, L.Cheng, J. Biol. Chem., 251, 3306 (1976).
5. Thus all attempts to conduct ammonolysis on ethyl 2-bromo-3-butenoate led to very complex mixtures mainly resulting from conjugation to give ethyl 2-amino-2-butenoate.[6]
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7. L.N.Owen, M.U.S.Sultanbawa, J. Chem. Soc., 3089 (1949). This result was later confirmed: H.Moureau, P.Chovin, M.Ducros, Bull. Chem. Soc. Fr., 586 (1953).
8. It is noteworthy that triethylamine was not useful in the conversion of (4) to (1) since the major reaction observed here was dehalogenation to give methyl β-methylcinnamate.
9. G.Faust, M.Verney, R.Vessiere, Bull. Chem. Soc. Fr., 2713 (1975).
10. Despite several attempts we have not been able to isolate intermediate (2) from the reaction of ammonia or other amine bases with (1) or (4) in DMSO.
11. This was prepared from 3,4-methylenedioxyacetophenone (G.Ciamician, P.Silber, Chem. Ber., 24, 2989 (1891)) and triethylphosphonoacetate in 73% yield according to: W.S.Wadsworth, W.D.Emmons, Org. Syn., 44, 45 (1965): mp 47-8°; nmr ($CDCl_3$):δ7.1-6.6(m,3H),6.02(s,1H),5.88(s,2H),4.15(q,2H,J=7Hz),2.48(s,3H),1.25 (t,3H,J=7Hz).

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