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Synthesis of 1-Aryl-2-Methyl-3-Ethoxycarbonyl-1,4,5,6-Tetrahydro-4(1H)-Pyridones and Their Derivatives

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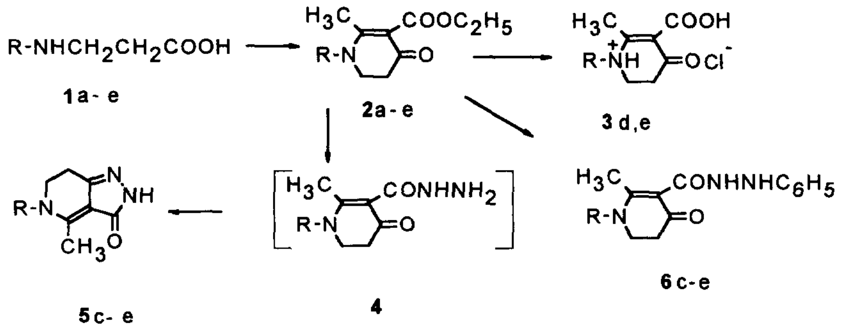
Abstract: Substituted derivatives of 4(1H)tetrahydropyridones have been synthesised by reaction of N-aryl-β-alanines with ethyl acetoacetate, their hydrolysis and interaction with hydrazine, phenylhydrazine have been investigated. Copyright © 1996 Elsevier Science Ltd

Besides of direct use N-aryl substituted β-amino acids are intermediate products in synthesis of many heterocyclic systems. On their basis compounds of azetidinone[1], quinolone[1,2], diazepine[3], imidazole[4], dihydropyrimidindione[5] class are synthesised.

In this work we have broadened the area of application of N-substituted β-amino acids for synthesis of heterocyclic compounds by presenting method of synthesis of 1-aryl-2-methyl-3-ethoxycarbonyl-1,4,5,6-tetrahydro-4(1H)-pyridones.



a R=4-CH_3-C_6H_4 , b R=4-CH_3O-C_6H_4 , c R=4-Br-C_6H_4 , d R=2,4-$(CH_3)_2$-C_6H_3 , e R=2,5-$(CH_3)_2$-C_6H_3

We have determined that N-aryl-β-alanines **1a-e** with excess of ethyl acetoacetate and catalytic amount of hydrochloric acid under reflux in toluene with separation of the forming water give respective tetrahydropyridones **2a-e.** Compounds 2 can be separated from the reaction mixture by flash chromatography or by extraction with ether from the reaction mixture treated with aqueous solution of sodium carbonate. 1-Aryl-2-methyl-3-ethoxycarbonyl-1,4,5,6-tetrahydro-4(1H)-pyridones **2** are white, crystalline substances well soluble in most organic solvents. In order to prove structure of the synthesised compounds **2** we have carried out some of their chemical transformations. Heating tetrahydropyridones **2** in diluted hydrochloric acid hydrolysis of ester group takes place and as a result respective acids **3** have been separated in the form of hydroclorides of tetrahydropyridones. Boiling tetrahydropyridones **2** with hydrazine hydrate in toluene new bicyclic compounds 5-aryl-4-methylpyrazolo [4,3-c] pyridin-3-ones **5**, that we think form because of cyclization of products of intermolecular hydrazinolysis **4**, have been got. Using phenylhydrazine in this reaction instead of hydrazine hydrate only products **6** of condensation of phenylhydrazine with ester group have been obtained.

All new compounds were characterised by NMR as well as by elemental analysis. Physical data for the compounds are given below.

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6. **2a** m. p. 179-181°C. Yield 12 %. ^{1}H-NMR ($CDCl_3$) : δ = 1,20 (3H, t, $CH_2\underline{CH_3}$), 1,88 (3H, s, 2-CH_3), 2,32 (3H, s, 4'-CH_3), 2,56 (2H, t, CH_2CO), 3,88 (2H, t, NCH_2), 4,2-4,4 (2H, m, OCH_2), 7,0-7,4 (4H, m, ArH).
7. **2b** m. p. 145-146°C. Yield 11 %. ^{1}H-NMR ($(CD_3)_2CO$) : δ = 1,09 (3H, t, $CH_2\underline{CH_3}$), 1,76 (3H, s, 2-CH_3), 2,39 (2H, t, CH_2CO), 3,81 (3H, s, OCH_3), 3,6-3,9 (4H, m, NCH_2+OCH_2), 6,9-7,3 (4H, m, ArH).
8. **2c** m. p. 220-221°C. Yield 5 %. ^{1}H-NMR ($CDCl_3$) : δ = 1,22 (3H, t, $CH_2\underline{CH_3}$), 1,89 (3H, s, 2-CH_3), 2,55 (2H, t, CH_2CO), 3,81 (2H, t, NCH_2), 4,21 (2H, dd, OCH_2), 7,04 and 7,49 (4H, 2d, ArH).
9. **2d** m. p. 122-123°C. Yield 27 %. ^{1}H-NMR (DMSO-d_6) : δ = 1,22 (3H, t, $CH_2\underline{CH_3}$), 1,78 (3H, s, 2-CH_3), 2,18 (3H, s, 2'-CH_3), 2,32 (3H, s, 4'-CH_3), 2,47 (2H, t, CH_2CO), 3,6-3,9 (2H,m, NCH_2), 7,0-7,3 (3H, m, ArH).
10. **2e** m. p. 99-100°C. Yield 43 %. ^{1}H-NMR (DMSO-d_6) : δ = 1,23 (3H, t, $CH_2\underline{CH_3}$), 1,77 (3H, s, 2-CH_3), 2,18 (3H,s, 2'-CH_3), 2,25 (3H, s, 4'-CH_3), 2,50 (2H, t, CH_2CO), 3,68 (2H, t, NCH_2), 4,12 (2H, dd, NCH_2), 7,1-7,3 (3H, m, ArH).
11. **3d** m. p. 164-165°C. Yield 71 %. ^{1}H-NMR (DMSO-d_6) : δ = 1,71 (3H, s, 2-CH_3), 2,08 (3H, s, 2'-CH_3), 2,19 (3H, s, 4'-CH_3), 2,5-2,8 (2H, m, CH_2CO), 3,6-3,9 (2H, m, N-CH_2), 5,41 (1H, s, $^+$NH), 7,0-7,3 (3H, m, ArH).
12. **3e** m. p. 190-192°C. Yield 68 %. ^{1}H-NMR (TFA) : δ = 1,67 (3H, c, 2-CH_3), 1,79 (3H, c, 2'-CH_3), 1,93 (3H, c, 5'-CH_3), 2,5-2,9 (2H, m, CH_2CO), 3,6-3,9 (2H, m, NCH_2), 5,49 (1H, c, $^+$NH), 6,54 and 6,85 (3H, 2s, ArH).
13. **5c** m. p. 135-137°C. Yield 76 %. ^{1}H-NMR (TFA) : δ = 2,17 (3H, s, 2-CH_3), 3,07 (2H, t, CH_2CO), 4,02 (2H, t, NCH_2), 6,78 and 7,40 (4H, 2d, ArH).
14. **5d** m. p. 298-299°C. Yield 78 %. ^{1}H-NMR (DMSO-d_6) : δ = 1,94 (3H, s, 2-CH_3), 2,09 (3H, s, 2'-CH_3), 2,17 (3H, s, 4'-CH_3), 2,6-2,9 (2H, m, CH_2CO), 3,5-3,9 (2H, m, NCH_2), 7,0-7,2 (3H, m, ArH), 10,31 (1H, s, NH).
15. **5e** m. p. 282-283°C. Yield 70 %. ^{1}H-NMR (DMSO-d_6) : δ = 1,99 (3H, s, 2-CH_3), 2,05 (3H, s, 2'-CH_3), 2,23 (3H, s, 5'-CH_3), 2,6-2,9 (2H, m, CH_2CO), 3,4-3,8 (2H, m, NCH_2), 7,0-7,3 (3H, m, NH), 10,41 (1H, s, NH).
16. **6c** m. p. 260-261°C. Yield 66 %. ^{1}H-NMR (TFA) : δ = 2,18 (3H, s, 2-CH_3), 3,05 (2H, t, CH_2CO), 4,02 (2H, t, NCH_2), 6,7-7,7 (9H, m, ArH).
17. **6d** m. p. 197-199°C. Yield 40 %. ^{1}H-NMR ($CDCl_3$) : δ = 2,06 (3H, s, 2-CH_3), 2,13 (3H, s. 2'-CH_3), 2,24 (3H, s, 4'-CH_3), 2,7-3,1 (2H, m, CH_2CO), 3,5-3,9 (2H, m, NCH_2), 6,8-8,2 (8H, m, ArH).
18. **6e** m. p. 197-199°C. Yield 36.8 %. ^{1}H-NMR (TFA) : δ = 1,90 (3H, s, 2-CH_2), 1,99 (3H, s, 2'-CH_3), 2,15 (3H, s, 5'-CH_3), 2,9-3,4 (2H, m, CH_2CO), 3,7-4,2 (2H, m, NCH_2), 6,6-7,8 (8H, m, ArH).

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