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A RAPID AND EFFICIENT SYNTHESIS OF IMIDAZO [1,2-a] and 1,2,4-TRIAZOLO [4,3-a]-PIPERAZINE CARBOXYLIC ACIDS.

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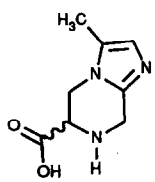
Abstract : A simple and general synthesis of novel cyclic α-amino acids by a route employing an easily accessable protected piperazine carboxylic acid imino-ether is described.

As part of a programme aimed at the synthesis of novel piperazine heterocycles as potential therapeutic agents , we required access to the previously unknown imidazo [1,2-a] and 1,2,4-triazolo [4,3-a] piperazine-6-carboxylic acids (**1**), (**2**) and (**3**):



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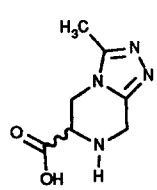

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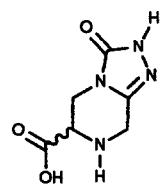

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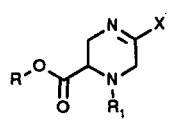
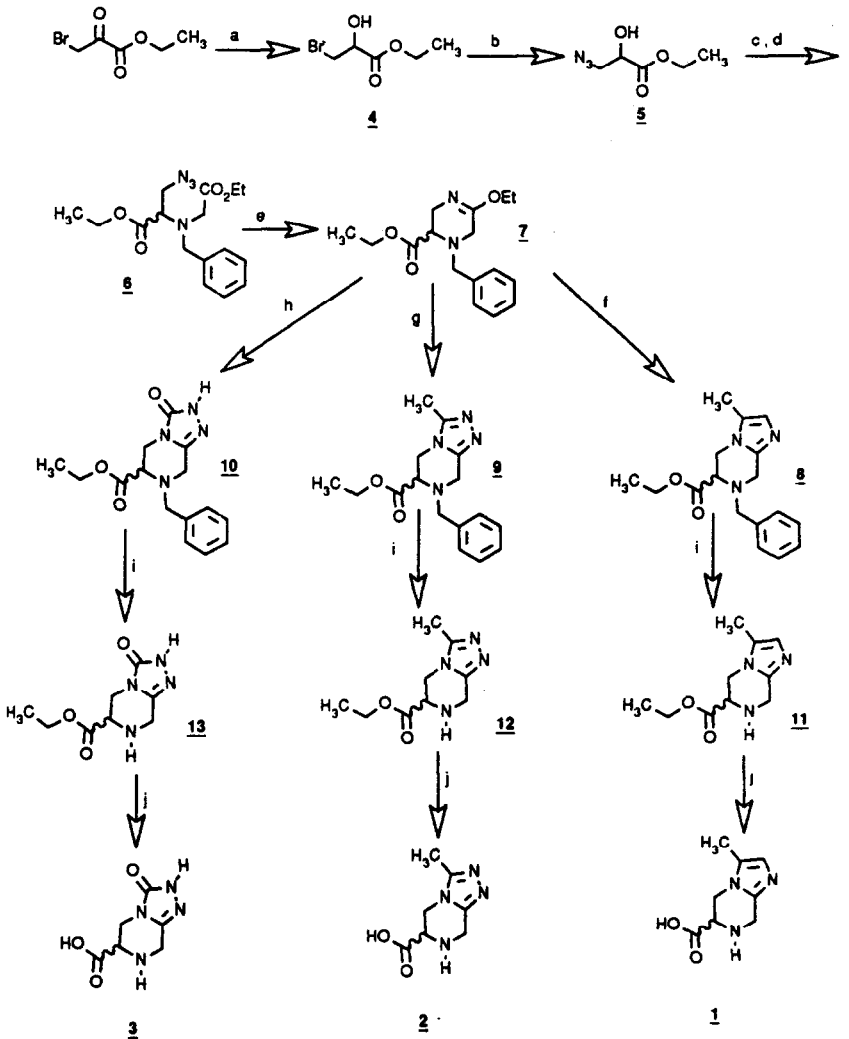
A general and efficient synthesis of this family of heterocyclic α-amino acids presents a certain synthetic challenge . After having attempted several routes starting from the aromatic heterocycles themselves using various protected aziridine-carboxylate or β-iodo-alanine derivatives , we reasoned that heterocyclization of an intermediate like **7** with an appropriate reagent would form the desired bicyclic α-amino acids in an easier , more direct manner .



7 | X=OCH_2CH_3
R=CH_2CH_3
R_1=CH_2-C_6H_5



(a) $NaBH_3CN$, MeOH pH 4, O°C, 90 mn.; (b) 1.5 mol. equiv. , NaN_3, EtOH/H_2O 1:1, 75°C 17 h; (c) ($F_3CSO_2)_2O$, 1 mol.equiv., lutidine, 2 mol. equiv.,CH_2Cl_2, O°C, 15 mn.; (d) $C_6H_5CH_2NHCH_2CO_2C_2H_5$, 2 mol.equiv.,$CH_2Cl_2$, 0 to 20°C , 90 mn. (e) $P(C_6H_5)_3$, 1 mol.equiv., anhydrous toluene, 100°C, 9 h; (f) $HC{\equiv}C\text{-}CH_2NH_2$, anhydrous toluene, 100°C, 7 h.; (g) $CH_3CONHNH_2$, 1 mol.equiv., EtOH 55°C, 24 h then toluene reflux 9h.; (h) $C_2H_5O_2CNHNH_2$, 1.1 mol.equiv., EtOH 55°C, 24h. , then toluene reflux 9h.; (i) H_2, 1 atm.$Pd(OH)_2$ EtOH, 40°C, 20-24 h.; (j) HCl 4 N , reflux 4-7 h.

We describe here a novel approach toward the preparation of the previously unreported imino-ether **7** . This key intermediate was prepared by intramolecular cyclization of the azido-diester **6** by triphenylphosphine . Reaction of **7** with various bifunctional molecules gives the targeted heterocyclic amino-acid derivatives with yields of 65-95 % .

Ethyl bromo-3-pyruvate was first reduced to ethyl 3-bromo,2-hydroxy propionate **4** (Figure 1) by sodium cyanoborohydride in MeOH at 0°C , pH 4 (58 % yield)[2]. An azide group was then cleanly introduced at position 3 by heating (75°C) with sodium azide in ethanol / H_2O (90% yield). The alcohol function of **5**[3] was next activated using trifluoromethanesulfonic anhydride / lutidine[4] in CH_2Cl_2 at 0°C for 15 minutes and the resulting triflate was condensed in situ with ethyl N-benzyl glycine (2 eq., 0 to 20°C) affording the azido diester **6**[5] with a 78 % yield after flash chromatography. Cyclization of **6** was carried out by an Aza-Wittig reaction using triphenylphosphine affording **7** in 58% yield . Heterocyclization of the imino-ether **7** using an excess of propargylamine[6] in toluene (100°C) provided the N-protected 3-methyl-imidazo [1,2-a]piperazine ester **8**[7] with an isolated yield of 65% . Likewise , reaction of **7** with acetic hydrazide (1eq.) or ethyl carbazate[9] (1.1 eq.) gave the 3-oxo-1,2,4-triazolo [4,3-a] piperazine ester **9**[10] (95% yield) and the 3-methyl 1,2,4-triazolo[4,3-a] piperazin-3-one ester **10**[11] (94% yield), respectively .The N-blocked intermediate **8** , **9** and **10** were then debenzylated under 1 atm. H_2 in EtOH at 40°C using 20% $Pd(OH)_2$ on charcoal (80% yields). The amino-esters **11** , **12** and **13** were then hydrolyzed with HCl 4N at reflux for 4-7 hours providing the targeted racemic amino - acids **1**[12] , **2**[13] and **3**[14] with yield of 80-85 % after crystallization from EtOH .

This new procedure presents a wide synthetic potential for the rapid preparation of a variety of novel bicyclic amino-acids for incorporation into peptides or the development of new therapeutic agents.

References and notes

1. ^1H and ^{13}C NMR analysis were performed on a 200 MHz Bruker AC 200 , IR spectra were recorded on a Perkin- Elmer 297 instrument, mass spectra on a Finnigan MAT-311A (-70eV) , and melting points (uncorrected) on a Thomas Hoover apparatus (capillary). Imino-ether **7** : colourless oil: ^1H NMR ($CDCl_3$) δ: 1.22 (t, J=7.0, 3H), 1.28 (t, J=7.0, 3H), 3.12 (d , J=14.5, 1H) , 3.4 (t, J=4.1, 1H), 3.49 (d ,J=14.5 ,1H), 3.70-3.90 (m , 4H) , 4.04 (dq, J=7.0 , 1.3 , 2H) , 4.18 (q, J=7.0 , 2H), 7.18-7.39 (m , 5H);^{13}C NMR ($CDCl_3$) δ : 171.9, 161.4 ,137.4, 128.9, 128.4, 127.4, 114.2, 60.5, 60.4, 58.9, 57.3, 49.1, 47.7 ; IR(neat, cm^{-1}) 1730, 1670; mass (CI): $C_{15}H_{22}N_2O_3$: m/e = 290
2. J.A.Peliska and M.H. O'Leary, *Biochemistry* ,**28** , 1604 (1989).
3. Ethyl 3-azido-2-hydroxy-propionate **5** ;colorless liquid :^1H NMR ($CDCl_3$) δ :1.36 (t, J=7.0, 3H): 3.60 (dd, J=16.0,1.5, 2H): 4.33(q, J=7.0 ,2H): 4.40 (m,1H);^{13}C NMR ($CDCl_3$) δ:172.3, 70.5, 62.3, 53.9, 14.1, .IR(neat,cm^{-1}) 3460(br), 2105, 1735, 1215, 1115.
4. Similar condensations of secondary amines and hydrazine derivatives with α-hydroxy esters have been reported by (a) R.V. Hoffman and H.O. Kim, *Tetrahedron Lett.*,**31**,2953 (1990).(b) F. Effenberger, U. Burkard and J.Willfahrt, *Angew. Chem. Int. Ed. Eng.*,**22** ,65,(1983).

5. Azido-diester **6** ; colorless oil :^{1}H NMR δ :1.21 (t, J=7.0 , 3H): 1.29 (t, J=7.0, 3H): 3.5 (s, 2H): 3.52-3.67 (m, 3H), 3.87 (d, J=14.5, 1H), 4.03 (d, J=14.5, 1H), 4.13 (q, J=7.0, 2H), 4.24 (dq, J=7.0,1.3, 2H), 7.18-7.45 (m, 5H);^{13}C NMR ($CDCl_3$) δ: 171.2, 170.5, 138.2, 128.9, 128.4, 127.5, 62.6, 61.0, 60.6, 56.5, 52.3, 50.7, 14.4, 14.2, ; IR (neat, cm^{-1}) :2110, 1730, 1025.

6. J.P Maffrand, D. Frehel, F. Eloy, D. Aubert, J.C. Ferrand. *Eur. J. Med. Chem.***10,**(5),528,(1975) and G.P. Claxon, J. Grisar,N.L. Wiech, *J. Med. Chem.***17** (3),364 (1974).

7. Imidazole **8** ;colorless oil :^{1}H NMR ($CDCL_3$) δ : 1.28 (t, J=7.0, 3H): 2.17 (s, 3H): 3.81-4.05 (m, 6H): 4.11-4.30 (m, 3H): 6.75 (s, 1H): 7.28-7.51 (m, 5H); ^{13}C NMR ($CDCL_3$) δ : 170.3, 141.5, 137.5, 128.9, 128.2, 125.8, 125.7, 125.0, 87.9, 61.2, 58.6, 57.6, 47.5, 43.7, 14.3 .

8. D.R. Shridhar,M. Jogibhukta, P.P. Joshi, P.G. Reddy, *Ind. J. Chem.* **20 B**, 132 (1981).

9. C.V. Reddy-Sastry, V.S. Krishnan, G.K. Narayan and K. Vermana. *Chem. Ind-London,* **7** , 227 (1989).

10. Triazole **9** pale yellow cristals (mp= 99-100°C):^{1}H NMR ($CDCl_3$) δ: 1.32 (t, J=7.0), 3H), 2.41 (s, 3H), 3.64-4.30 (m, 9H),7.35 (s,5H); ^{13}C NMR ($CDCl_3$) δ: 169.5, 149.7, 148.7, 136.9, 129, 128.7, 127.9, 61.6, 58.6, 56.8, 45.1, 43.5, 14.3, 10.1.

11. Triazolone **10** , light-yellow oil ; ^{1}H NMR ($CDCl_3$) δ:1.32 (t, J=7.0, 3H), 3.67-4.35 (m , 9H), 7.35(s, 5H); 10.31 (br, 1H);^{13}C NMR ($CDCl_3$) δ : 169.5, 154.6, 142.6, 136.7, 128.9, 128.7, 128.0, 61.5, 58.7, 56.7, 44.7, 41.2, 14.3 .

12. (±)3-methyl-5,6,7,8-tetrahydro-imidazo[1,2-a] pyrazine-6-carboxylic acid **1**, amorphous white solid, mp =250-255°C; ^{1}H NMR ($CDCl_3$) δ: 2.34 (s, 3H), 4.26-4.80 (m, 5H), 7.49 (s, 1H);^{13}C NMR (DMSO) δ:166.5, 136.0, 130.3, 116.0, 51.9, 41.1, 7.8 ; HRMS : calculated for 181.0851 (m^{+}) ; found 181.0852.

13. (±) 3-methyl-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyrazine -6-carboxylic acid **2**, mp = 235-239°C ;^{1}H NMR (DMSO) δ:2.67(s, 3H),4.36-4.85 (m, 5H);^{13}C NMR (DMSO) δ:166.5, 151.5, 145.6, 51.8, 41.4, 40.7, 9.1; HRMS : calculated for 182.0804 (M^{+}): found 182.0804.

14. (±)3-oxo-5,6,7,8-tetrahydro-2H-1,2,4-triazolo[4,3-a]pyrazine -6-carboxylic acid **3**, amorphous white solid, mp= 229-234°C; ^{1}H NMR (DMSO) δ: 3.76 (dd, J=12.5, 10.3, 1H), 4.02 (dd, J=12.5, 5.1, 1H), 4.20 (d, J=16.2, 1H), 4.32 (d, J=16.2, 1H), 4.70 (dd, J=10.3, 5.1, 1H); ^{13}C NMR (DMSO) δ :166.7, 153.4, 137.4, 52.1, 38.0, 37.9 ; HRMS: calculated for $C_6H_8N_4O_3$ (M^{+}): 184.0596; found : 184.0598

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