Pergamon

Tetrahedron Letters, Vol. 36, No. 31, pp. 5637-5640, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01034-5

Unexpected Pyrazolo[4,3-*d*][2,3]benzodiazepine Synthesis from 1-(N,N-Diaroyl)amino-4-phenyl-[1,2,3]triazol-5-yl-methyltriphenylphosphonium bromide via Tandem Phosphorylide Formation and Subsequent Dimroth-like Rearrangement of the Triazole Ring

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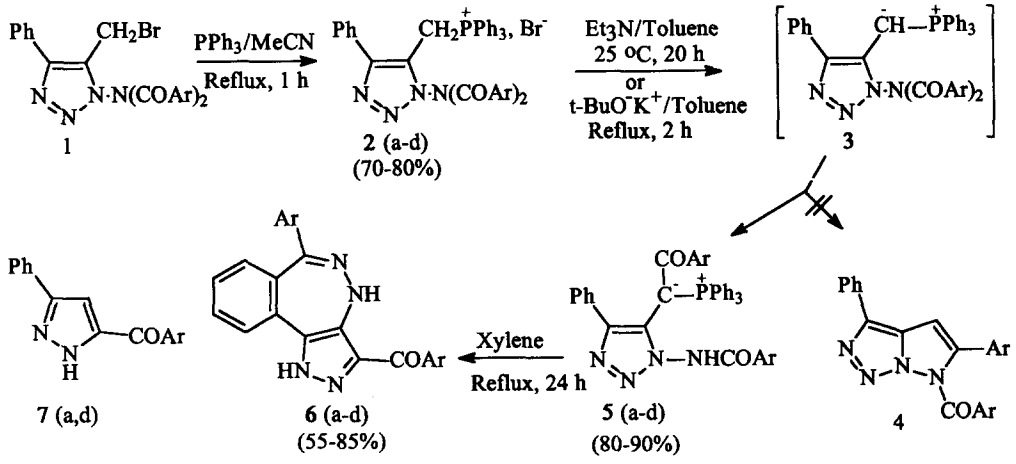
Abstract. 1-(N,N-Diaroyl)amino-4-phenyl-1,2,3-triazol-5-yl-methyltriphenylphosphonium bromide **2** reacted with potassium *t*-butoxide or triethylamine in dry toluene giving the very stable phosphorus ylide **5**. Refluxing of **5** in xylene gave the unexpected 3-aroyl-6-aryl-pyrazolo[4,3-*d*][2,3]benzodiazepines **6** by a Dimroth-like rearrangement of the triazole ring and a 1,7-electrocyclization of the nitrilimine intermediate **11**. When the xylene solution was not rigorously refluxed the 3(5)-aroyl-5(3)-phenyl pyrazole **7** was isolated. The x-ray crystal structures of compounds **5d** and **6b** are also given.

In continuation of our work[1,2] on the synthesis of condensed *v*-triazolo-heterocycles, some 1-(N,N-diaroyl)amino-4-phenyl-*v*-triazol-5-yl-methyltriphenylphosphonium bromides **2** were prepared by reacting the corresponding 5-bromomethyl-*v*-triazoles **1** with triphenylphosphine, aiming to synthesize the analogous phosphorus ylides **3**. The later were expected to give upon a Wittig-type reaction the fused *v*-triazolo-pyrazole ring system **4**, by analogy to the reported[3,4] synthesis of various indole derivatives from 2-acylamino-benzyltriphenylphosphonium salts.



1 → 2 (a-d) (70-80%) → 3 → 5 (a-d) (80-90%) → 6 (a-d) (55-85%) + 7 (a,d) + 4

a) Ar = C_6H_5 b) Ar = *p*-Cl-C_6H_4 c) Ar = *o*-Cl-C_6H_4 d) Ar = *p*-MeO-C_6H_4

However, treatment of the phosphonium salts **2** with triethylamine in dry toluene at 25 °C afforded in high yields (80-90%) the very stable phosphorus ylides **5** as white crystalline compounds. Compounds **5** were also obtained in very good yields by refluxing **2** with potassium *t*-butoxide in dry toluene. The formation of **5** in the last case at higher temperatures is attributed to solubility reasons, since at 25 °C both, the phosphonium salts and the *t*-BuO⁻K⁺ are insoluble in toluene. The structure of **5** was elucidated by means of their spectroscopic characteristics[5] and confirmed by x-ray crystallographic analysis carried out in **5d** (Figure 1)[6].

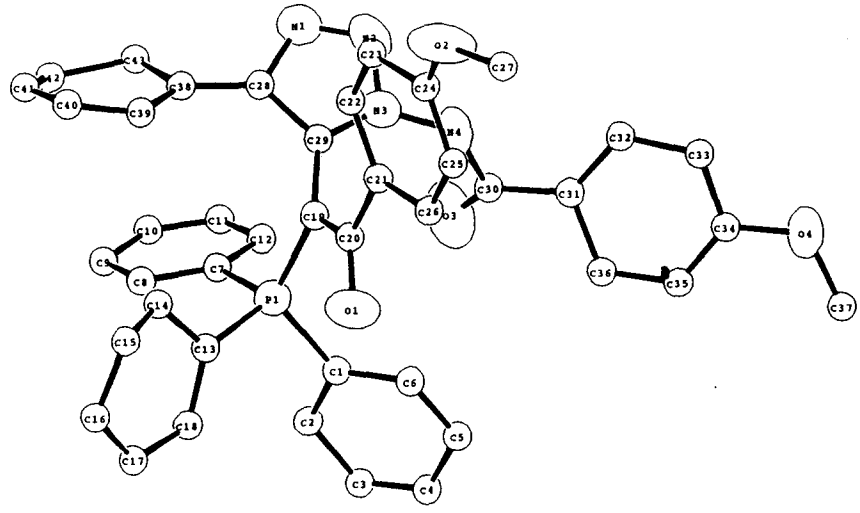
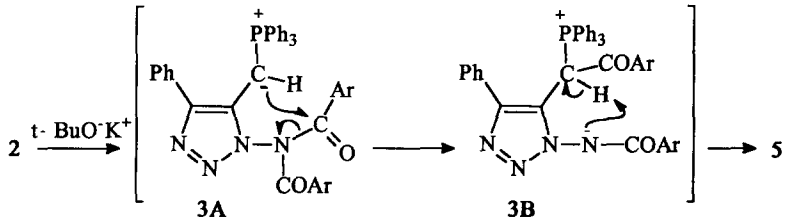


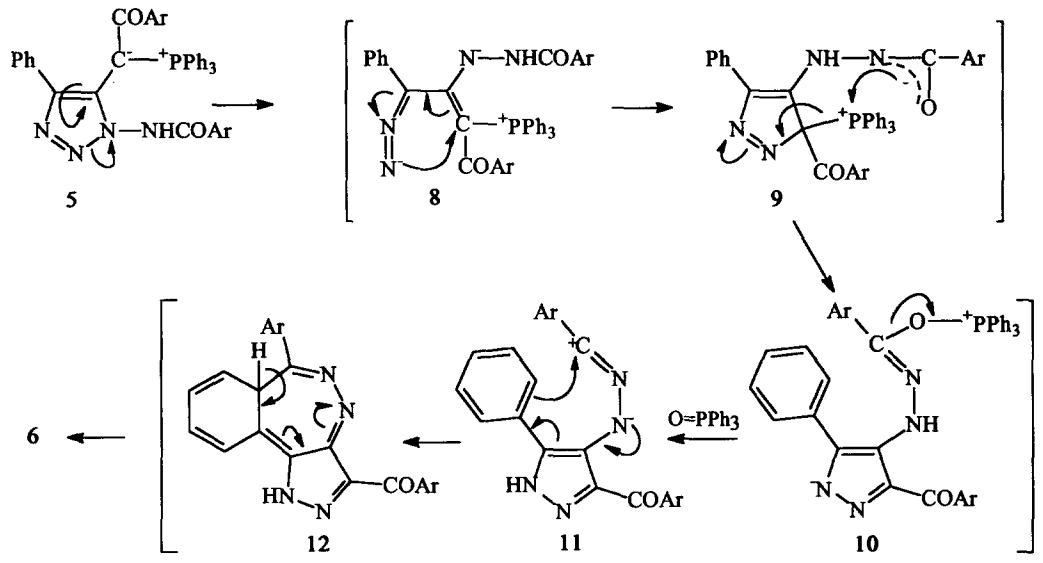
Figure 1. x-Ray molecular structure of 5d[6]

Compounds **5** are most probably formed from the phosphorylide **3A**, which first should be formed upon the action of the base to the phosphonium salt **2**. Attack of the ylide carbon of **3A** on the carbonyl carbon of the aroyl group, instead of giving the Wittig reaction product **4**, causes the splitting of the weak N-CO bond, thus giving, under an aroyl group migration from nitrogen to carbon and a subsequent proton shift, the very stable phosphoranes **5**.



Compounds **5** when refluxed in xylene (bp. 140-142 °C) gave in good yields (55-85%) the unexpected pyrazolo[4,3-*d*][2,3] benzodiazepines **6** as yellow crystals. When the xylene solution was not rigorously refluxing (inner temperature of the solution ~130-135 °C), instead of compounds **6** the 3-aroyl-5-phenyl-pyrazoles **7** were isolated, along with a mixture of other , not yet identified, compounds. It is interesting to note however that, when compounds **5** were refluxed in chlorobenzene (bp. 130-132 °C) the same compounds **6** in good yields were isolated, although over a longer reaction time (48 h).

The formation of **6** from **5** requires an opening of the triazole ring and a recyclization to the pyrazole intermediate **9** in a Dimroth-like[7,8] rearrangement. A subsequent migration of the triphenyl-phosphine group from carbon to oxygen might generate the pyrazole anion **10** with an enol oxy-phosphonium structure[9,10] of the hydrazonoyl side chain. Elimination of the triphenylphosphine oxide group would led to the formation of the nitrilimine intermediate **11**, which may undergo a 1,7-electrocyclization[11] (8π electron) followed by a sigmatropic [1,5] hydrogen shift, thus giving rise to the formation of the benzodiazepine ring system.



The dependence of the path of the reaction on the temperature and on the solvent used should be noted. It seems likely that the Dimroth rearrangement, which is necessary for the formation of both, **6** and **7**, takes place at temperatures 120-130 °C and is independent of the polarity of the solvent. The cyclization to the benzodiazepine ring however requires a temperature of at least 140 °C when the reaction is performed in the non polar hydrocarbons, such as xylene, whereas in the more polar chlorobenzene this cyclization occurs at 130-132 °C. At the intermediate temperatures of 130-135 °C, and when the reaction was carried out in xylene, the pyrazole **7**, but not **6**, was isolated, and this behaviour might be the result of the polar intermediates, such as **9-11**, that participate in the formation of **6**, which require a higher temperature and/or a more polar solvent for their formation and stabilization. It is not possible for the moment to propose any mechanism for the formation of **7**, since we were not yet able to isolate and identify all the products of this reaction, which however is under further investigation.

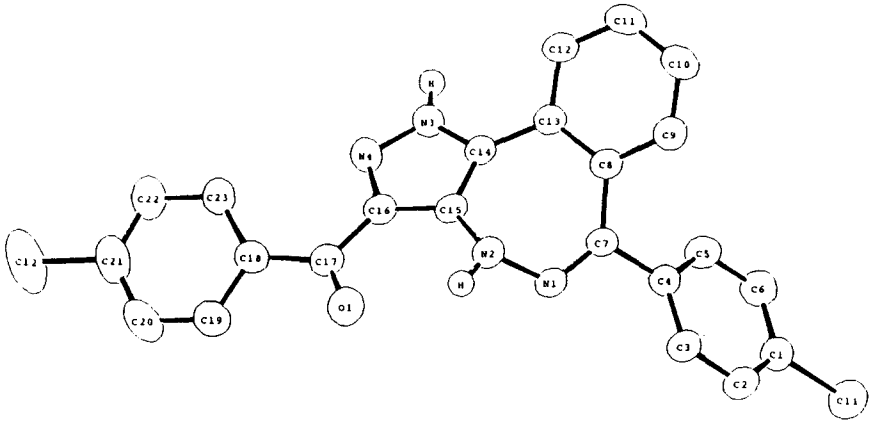


Figure 2. x-Ray molecular structure of **6b**[13]

The structure of compounds **6** and **7** was established on the basis of their spectroscopic data[12,13] and for the pyrazolo-benzodiazepines **6** was also confirmed by x-ray crystallographic analysis performed in compound **6b** (Figure 2)[14].

Acknowledgements. One of us, E. L., wish to thank the State Scholarship Foundation of Greece for a financial support.

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5. Spectral data for compound **5d**: m.p. 228-229 °C; **5d** + DMSO: $C_{41}H_{35}N_4O_4P+C_2H_6OS$: MW = 780.790: Calc (%): C=69.22, H=5.29, N=7.17; Found (%): C=69.17, H=5.34, N=6.71; IR: 3600, 1680 cm^{-1}; ^{1}H-NMR (300 MHz): 3.75, 3.91 (two s, 6H, MeO), 6.78 (bs,2H), 6.84 (d, 2H), 6.96 (m, 4H), 7.51 (d, 2H), 7.23-7.36 (m, 4H), 7.50-7.60 (m,12H), 7.69-7.72 (m, 2H), 11.7 (s, 1H); ^{13}C-NMR (75 MHz): 51.7 (d, 121.1 Hz), 55.0, 55.5, 132.8 (d, 15.2 Hz), 143.0 (d, 4 Hz); 4-Ph: 126.55, 127.2, 127.7, 136.3; *p*-MeO-C_6H_4CONH: 113.7, 123.4, 130.25, 160.1, 165.9 (CO); *p*-MeO-C_6H_4COC=P: 113.1, 128.9, 133.13 (d, 10.9 Hz), 162.7, 184.7 (d, 5.5 Hz, CO); MS: m/z (%) 552 (0.3), 424 (6, M-Ph_3PO), 278 (59), 277 (100), 262 (30), 201 (27), 199 (22), 183 (39), 152 (18), 135 (30), 108 (11), 103 (96), 77 (23).
6. Crystallographic data for **5d**: Compound **5d** was co-crystallized with a solvent (DMSO) molecule; $C_{45}H_{41}N_4O_5PS$: MW = 780.8, space group $P\bar{1}$, a=11.1518(8), b=12.7206(9), c=14.85365(12) Å, α=101.1661(2), β=99.382(3), γ=90.072(2)°, V=2038.4(3) $Å^{-3}$, Z=2, C_{calcd}/D_{meas}: 1.262/1.23 $Mg.m^{-3}$, λ(Mo Ka)=0.71070, T=298 °K, μ=0.169 mm^{-1}, F(000)=808, Scan mode/speed: θ-2θ/3.0 (°/min), θ=1.42 to 25.00 °, final R=0.0754 for 7169 reflections. Crystallographic data have been deposited at the Cambridge Crystallographic Data Center.
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12. Spectral data for compound **6d**: IR: 3295, 1620 cm^{-1}; ^{1}H-NMR (300 MHz): 3.80, 3.89 (two s, 6H, MeO), 6.82 (d, 8.5, 2H), 6.98 (d, 8.6, 2H), 7.03 (d, 7.8, 1H, 7-H), 7.13 (d, dd as t, 7.6, 1H, 8-H), 7.31 (d, 8.5, 2H), 7.42 (dd as t, 7.6, 1H, 9-H), 7.60 (d, 7.6, 1H, 10-H), 7.74 (bm, 2H), 8.54 (s, 1H, NH). 13.5 bs, 1H, NH); ^{13}C-NMR (75 MHz): 55.15, 55.37, 113.24, 113.41, 125.24, 126.59, 129.78, 130.12, 130.22, 132.11, 132.38, 134.53, 139.67, 159.54, 159.95, 163.23; MS: m/z (%) 424 (M^+, 27), 423 (M-1, 100), 408 (15), 394 (3), 368 (5), 237 (7), 212 (4), 135 (54), 134 (4), 103 (3), 92 (18).
13. Spectral data for compound **7d**: IR: 3300, 3190, 3100, 1620 cm^{-1}; ^{1}H-NMR (300 MHz): 3.88 (s,3H, MeO), 7.00 (d, J=8.9Hz, 2H), 7.13 (s, 1H, H-4), 7.31 (m, 1H), 7.35 (m, 2H), 7.79-7.82 (m, 2H), 8.13 (d, J=8.9 Hz, 2H); ^{13}C-NMR (75 MHz): 55.53, 106.67 (d, 177.8, C-4), 113.92, 125.78, 128.51, 128.90, 129.77, 131.32, 132.1, 144.48 (C-3pz), 150.17 (C-5pz) 163.81, 184.33 (CO); MS: m/z (%) 278 (M^+, 16), 277 (12), 235 (8), 201 (15), 199 (9), 183 (11), 178 (15), 135 (54), 116 (8), 115 (16), 114 (20), 107 (11), 105 (14), 104 (13), 92 (37), 77 (100).
14. Crystallographic data for **6b**: $C_{23}H_{14}N_4Cl_2O$: MW = 433.28, space group $P2_1/c$, a=14.568(2), b=11.883(2), c=11.862(2) Å, β=101.234(4)°, V=2014.1(6) $Å^{-3}$, Z=4, C_{calcd}/D_{meas}: 1.429/1.40 $Mg.m^{-3}$, λ(Mo Ka)=0.71070, T=298 °K, μ=0.346 mm^{-1}, F(000)=888, Scan mode/speed: θ-2θ/1.5 (°/min), θ=1.43 to 25.00°, final R=0.0512 for 3545 reflections. Crystallographic data have been deposited at the Cambridge Crystallographic Data Center.

(*Received in UK* 16 *May* 1995; *revised* 7 *June* 1995; *accepted* 9 *June* 1995)