

P. Molina*, Ma. J. Vilaplana, and P. L. Andreu

Departamento de Química Organica, Facultad de Ciencias Químicas, Universidad de Murcia,
30001 Murcia, Spain

J. Møller

Department of Chemistry, Odense University,
DK-5230 Odense M, Denmark

Received March 2, 1987

N-Aryl-*N*-(α -phenylphenacyl)oxamoyl chlorides react with *N*³-arylsubstituted amidrazones to give functionalized 1,2,4-triazoles which undergo ring-closure by the action of thionyl chloride to give 1,2,4-triazolo[1,5-*a*]pyrazinium chlorides in excellent yields.

J. Heterocyclic Chem., **24**, 1281 (1987).

As part of an investigation on fused heterocycles, we have been engaged in the preparation of bridgehead nitrogen heterocycles which contain the 1,2,4-triazolo moiety, e.g. 1,2,4-triazolo[1,5-*a*]pyridine [1], 1,2,4-triazolo[1,5-*c*]quinazoline [2], 1,2,4-triazolo[5,1-*c*][1,2,4]triazine [3], 1,2,4-triazolo[4,3-*b*][1,2,4]triazole [4], pyrazolo[5,1-*c*][1,2,4]triazole [5] and 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole [6]. Recently, we have reported that *N*-aryl-*N*-(α -phenylphenacyl)oxamoyl chlorides react with unsubstituted amidrazones [7] and amines/acetic anhydride/perchloric acid [8] to give imidazo[2,1-*d*][1,2,4]triazines and oxazinium perchlorates respectively.

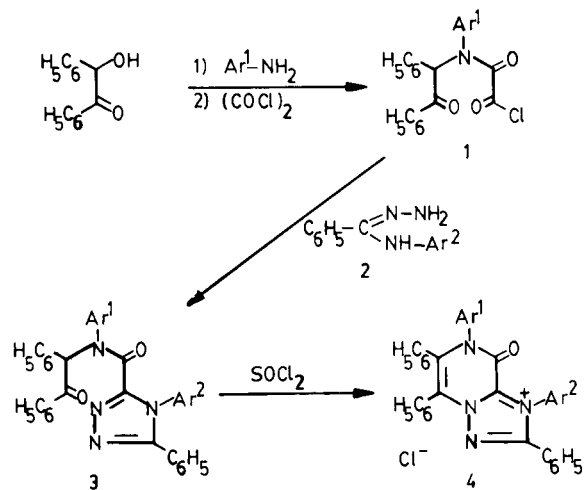
We report here a convenient preparation of otherwise not readily available 1,2,4-triazolo[1,5-*a*]pyrazine ring system which contain the pyrazine and 1,2,4-triazolo moieties. Our approach is based on the cyclization of the adequate open-chain precursor **1** to give the 1,2,4-triazole ring followed by annulation of the pyrazine ring onto the 1,2,4-triazole ring.

The methods described so far for the preparation of 1,2,4-triazolo[1,5-*a*]pyrazines involve either ring-closure of *N*-aminopyrazinium salts with carboxylic acids, anhydrides or acid chlorides [9]; cyclodehydration of 2-hydroxyiminomethyleneamino pyrazines with polyphosphoric acid [10]; or else oxidative ring-closure of *N*-(2-pyrazinyl) benzamides, available from 2-aminopyrazines and benzonitrile, with lead tetracetate [11]. However, no generally useful procedure for the preparation of 1,2,4-triazolo[1,5-*a*]pyrazinium cations has hitherto been reported.

N-Aryl-*N*-(α -phenylphenacyl)oxamoyl chlorides **1**, themselves readily available from benzoin by sequential treatment with aromatic amines and oxalyl chloride [8], react with *N*³-aryl-substituted amidrazones **2** in dry toluene at reflux temperature for 8 hours to give the corresponding functionalized 1,2,4-triazoles **3** in moderate to excellent yields (56-90%) (Table 1). Compounds **3** undergo ring-closure by the action of thionyl chloride to give 1,2,4-triazolo-

[1,5-*a*]pyrazinium chlorides **4a** in excellent yields (71-96%) (Table 2). These compounds when treated with tetrafluoroboric acid in ethanolic solution for a short period of time are converted into the corresponding tetrafluoroborates **4b** which are isolated in high state of purity.

Scheme 1



Compounds **3** and **4** are characterized on the basis of their elemental analysis and spectral data. The ir spectra of **3** show two strong bands at 1700 and 1650 cm⁻¹ attributable to the two carbonyl groups, whereas ir spectra of **4** show a strong absorption band at 1700 cm⁻¹ due to the carbonyl group of the pyrazine ring. The ¹³C nmr aided by INEPT of compounds **3** showed the CH signal at 67 ppm, two signals at δ 160 and 195 ppm indicated the presence of the two carbonyl groups. In the ¹H nmr spectra the methine proton appears at δ 5.45 ppm as a singlet. When heated in the ion source of the mass spectrometer the tetrafluoroborate salts **4b**, undergo thermolysis at 320-350° with formation of several products. The mass spectra of this mixture changes considerably with the heating rate

Table 1
Preparation of 1,2,4-Triazole Derivatives **3**

Entry	Ar ¹	Ar ²	Yield (%)	Mp °C	Molecular Formula	Analyses (%)					
						Calcd.			Found		
						C	H	N	C	H	N
a	C ₆ H ₅	4-Cl-C ₆ H ₄	64	268-271	C ₃₅ H ₂₅ N ₄ ClO ₂ 596.06	73.87	4.43	9.85	73.66	4.59	9.78
b	4-H ₃ C-C ₆ H ₄	C ₆ H ₅	61	242-244	C ₃₆ H ₂₈ N ₄ O ₂ 548.64	78.81	5.14	10.21	79.07	5.28	9.97
c	4-H ₃ C-C ₆ H ₄	4-Br-C ₆ H ₄	90	271-273	C ₃₆ H ₂₇ N ₄ BrO ₂ 627.54	68.90	4.34	8.93	69.12	4.28	9.07
d	4-H ₃ CO-C ₆ H ₄	4-Cl-C ₆ H ₄	61	273-275	C ₃₆ H ₂₇ N ₄ ClO ₃ 599.09	78.18	4.54	9.37	78.29	4.62	9.44
e	4-H ₃ CO-C ₆ H ₄	4-Br-C ₆ H ₄	56	275-277	C ₃₆ H ₂₇ N ₄ BrO ₃ 643.54	67.19	4.23	8.71	67.28	4.19	8.62
f	4-Cl-C ₆ H ₄	4-Cl-C ₆ H ₄	82	263-265	C ₃₅ H ₂₄ N ₄ Cl ₂ O ₂ 603.50	69.66	4.01	9.28	69.55	3.94	9.39
g	4-Cl-C ₆ H ₄	4-Br-C ₆ H ₄	82	257-259	C ₃₅ H ₂₄ N ₄ BrClO ₂ 647.96	64.88	3.73	8.65	64.93	3.59	8.61

Table 2
Preparation of 1,2,4-Triazol[1,5-a]pyrazinium Chlorides **4**

Entry	Ar ¹	Ar ²	Yield (%)	Mp °C	Molecular Formula	Analyses (%)					
						Calcd.			Found		
						C	H	N	C	H	N
a	C ₆ H ₅	4-Cl-C ₆ H ₄	84	344-347	C ₃₅ H ₂₄ N ₄ Cl ₂ O 587.51	71.55	4.12	9.54	71.66	4.21	9.66
b	4-H ₃ C-C ₆ H ₄	C ₆ H ₅	79	348-350	C ₃₆ H ₂₇ N ₄ ClO 567.09	76.25	4.80	9.88	76.39	4.93	9.73
c	4-H ₃ C-C ₆ H ₄	4-Br-C ₆ H ₄	95	349-351	C ₃₆ H ₂₆ N ₄ BrClO 645.99	66.73	4.04	8.65	66.77	4.22	8.48
d	4-H ₃ CO-C ₆ H ₄	4-Cl-C ₆ H ₄	85	236-238	C ₃₆ H ₂₆ N ₄ Cl ₂ O 617.54	71.64	4.34	9.28	71.77	4.39	9.43
e	4-H ₃ CO-C ₆ H ₄	4-Br-C ₆ H ₄	96	232-234	C ₃₆ H ₂₆ N ₄ BrClO ₂ 661.99	65.12	3.95	8.70	65.25	4.14	8.93
f	4-Cl-C ₆ H ₄	4-Cl-C ₆ H ₄	71	341-343	C ₃₅ H ₂₃ N ₄ Cl ₃ O 621.26	67.59	3.73	9.01	67.72	3.91	8.87
g	4-Cl-C ₆ H ₄	4-Br-C ₆ H ₄	75	338-340	C ₃₅ H ₂₃ N ₄ BrCl ₂ O 666.41	63.08	3.48	8.41	62.91	3.54	8.66

and sample size, probably due to secondary processes of the primary thermolysis products [12]. For this reason characterization of compounds **4b** on the basis of EI-mass spectrometry is difficult although several peaks in the spectra could be rationalized as molecular ions of reasonable thermolysis products of the tetrafluoroborate salts **4b**.

Application of Fast Atom Bombardment (FAB) mass spectrometry appeared in the first hand to be impossible due to difficulties in having these compounds dissolved in

an appropriate matrix. However, by adding a solution of compounds **4b** in trifluoroacetic acid to glycerol this problem was overcome. The FAB-spectra show relatively abundant ions at masses corresponding to the cations of the tetrafluoroborates **4b**, but no significant fragment ions.

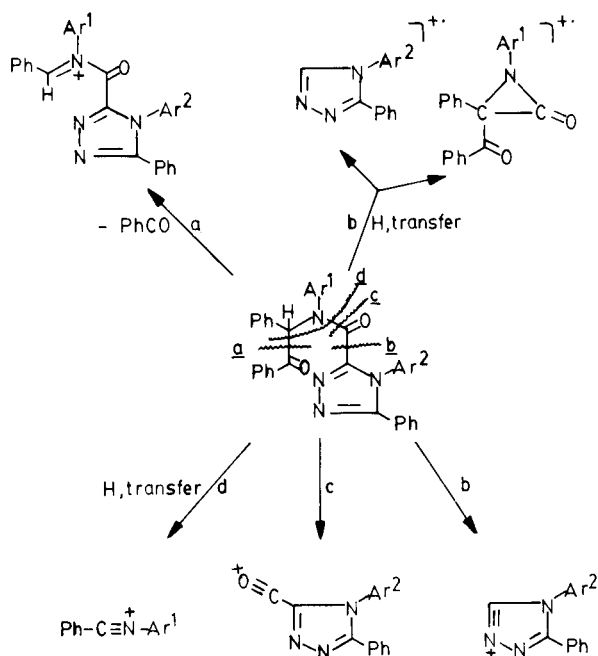
The EI-spectra of compounds **3**, obtained at samples temperatures of 210-250° are given in Table 3. Low abundant molecular ions are observed in all cases. The major fragmentations may be explained as shown in Scheme 2.

Table 3
Spectral Data of Compound **3** and **4**

Compound No.	IR (cm ⁻¹)	MS m/e (%) [a]
3a	1693, 1659, 1591, 1449, 1257, 1223, 1092, 849, 764, 696	570 (M + 2, 0.5), 568 (M ⁺ , 1.5), 542 (1), 526 (1), 524 (3), 465 (36), 464 (33), 463 (100), 451 (3), 449 (10), 313 (77), 284 (10), 282 (34), 256 (15), 255 (25), 254 (35), 180 (63), 165 (22), 153 (11), 151 (30), 105 (25), 77 (36)
3b	1693, 1653, 1597, 1512, 1466, 1449, 1431, 1256, 1224, 778, 764, 699	548 (M ⁺ , 3), 520 (2), 504 (3), 443 (90), 415 (15), 327 (100), 428 (28), 221 (20), 220 (18), 194 (61), 165 (15), 144 (18), 118 (27), 117 (40), 105 (35), 91 (38), 77 (30)
3c	1693, 1648, 1512, 1450, 1257, 1223, 1075, 979, 843, 764, 757, 723, 699	628 (M + 2, 2), 626 (M ⁺ , 2), 584 (1), 582 (1.5), 523 (90), 521 (90), 495 (5), 493 (5), 432 (12), 327 (100), 326 (14), 301 (16), 300 (24), 299 (16), 298 (22), 196 (20), 195 (24), 194 (72), 165 (18), 144 (20), 105 (26), 91 (28), 77 (28)
3d	1693, 1648, 1512, 1466, 1449, 1251, 1223, 1172, 1043, 843, 764, 702	600 (M + 2, 0.5), 598 (M ⁺ , 1.5), 572 (1), 570 (2.5), 556 (2), 554 (5), 495 (39), 494 (36), 493 (100), 451 (5), 449 (15), 343 (68), 284 (10), 282 (30), 257 (7), 256 (3), 255 (20), 254 (6), 210 (33), 196 (23), 180 (15), 178 (19), 165 (14), 154 (26), 153 (32), 143 (20), 105 (21), 77 (16)
3e	1693, 1648, 1512, 1461, 1450, 1302, 1251, 1223, 1172, 1070, 843, 832, 764, 758, 699	644 (M + 2, 2), 642 (M ⁺ , 2), 616 (1), 600 (2), 598 (2), 539 (97), 537 (100), 495 (20), 493 (19), 343 (90), 328 (30), 326 (32), 301 (18), 300 (16), 299 (18), 298 (16), 224 (10), 222 (11), 210 (31), 198 (39), 197 (24), 196 (40), 195 (23), 165 (21), 145 (17), 143 (17), 107 (38), 105 (34), 77 (29)
3f	1693, 1653, 1466, 1449, 1257, 1223, 1093, 843, 758, 696	606 (M ⁺ , 0.3), 604 (M + 2, 1.5), 602 (M ⁺ , 2), 576 (1.5), 574 (2), 560 (2.5), 558 (3.5), 501 (8), 499 (37), 497 (57), 490 (5), 488 (15), 349 (11), 347 (31), 284 (24), 282 (67), 256 (10), 255 (15), 254 (23), 216 (30), 214 (74), 180 (7), 178 (22), 153 (33), 151 (100), 114 (15), 112 (15), 105 (74), 77 (91)
3g	1693, 1670, 1466, 1449, 1353, 1257, 1223, 1070, 1013, 843, 736, 696	650 (M + 4, 1), 648 (M + 2, 4), 646 (M ⁺ , 3), 622 (1.5), 620 (5), 618 (4), 606 (1), 604 (5), 602 (4), 545 (14), 543 (65), 541 (42), 494 (13), 492 (13), 349 (20), 347 (57), 328 (36), 326 (35), 300 (28), 299 (20), 298 (27), 224 (18), 222 (17), 216 (36), 214 (100), 197 (45), 195 (44), 165 (13), 105 (57), 77 (92)
4a	1704, 1636, 1591, 1464, 1447, 1317, 1146, 1092, 1022, 750, 721, 694	554 (19), 553 (48), 552 (43), 551 (100)
4b	1698, 1639, 1599, 1548, 1509, 1482, 1462, 1446, 1325, 1314, 1146, 1027, 808, 765, 743, 697	533 (20), 532 (46), 531 (100)
4c	1699, 1636, 1551, 1466, 1448, 1319, 1145, 1070, 1024, 804, 750, 723, 713, 700	613 (13), 612 (40), 611 (100), 610 (47), 609 (49)
4d	1699, 1636, 1608, 1552, 1512, 1461, 1447, 1300, 1252, 1146, 1117, 1092, 1022, 841, 756, 733, 716, 696	584 (19), 583 (47), 582 (42), 581 (100)
4e	1699, 1630, 1608, 1552, 1512, 1464, 1300, 1252, 1179, 1146, 1064, 1026, 770, 750, 725, 714, 698	629 (18), 628 (42), 627 (100), 626 (48), 625 (95)
4f	1704, 1636, 1552, 1464, 1317, 1146, 1092, 1022, 806, 773, 756, 735, 689	589 (20), 588 (36), 587 (73), 586 (48), 585 (100)
4g	1704, 1636, 1552, 1466, 1315, 1146, 1090, 1070, 1024, 806, 773, 752, 731, 698	634 (17), 633 (32), 632 (43), 631 (100), 630 (32), 629 (76)

[a] Compounds **3** were recorded by EI-*ms* at 70 eV, and compounds **4** as tetrafluoroborates by FAB-*ms*. The discrepancies of the isotopic patterns from the theoretical values are due to contribution of isotopes of minor peaks one and two masses units below the masses of the cations and to background peaks. The relative intensity of the most abundant isotope of the cation is normalized to 100%. No significant fragment ions were observed.

Scheme 2



EXPERIMENTAL

The melting points were determined with a Kofler hot stage microscope and were uncorrected. The ir spectra were recorded on mineral oil mulls with a Nicolet-FT 5DX instrument. The proton nmr spectra were recorded with a Varian EM-360 M and ¹³C nmr spectra on a Bruker AC 200 spectrometer with TMS as internal standard. Elemental analysis were performed with a Perkin-Elmer 240 C instrument. The EI-mass spectra were obtained with a Hewlett-Packard 5993 C gc/ms system; compounds were introduced through the direct insertion probe. The FAB-mass spectra were determined on a Varian MAT 311 A instrument equipped with an Ion Tech FAB-11NF saddle field gun, using 8-9 kV argon atoms.

Preparation of 1,2,4-Triazole Derivatives **2**. General Procedure.

To a solution of the appropriate *N*-aryl-*N*-(α -phenylphenacyl)oxamoyl chloride **1** (2 mmoles) in dry toluene (20 ml), the corresponding *N*³-aryl-substituted amidrazone **2** (2 mmoles) was added. The reaction mixture was stirred at reflux temperature for 8 hours. After cooling, the precipi-

tated solid was collected by filtration and recrystallized from toluene to give **3** (Table 1).

Preparation of 1,2,4-Triazolo[1,5-*a*]pyrazinium Chlorides **4**. General Procedure.

A mixture of the appropriate 1,2,4-triazole **3** (3 mmoles) and thionyl chloride (15 ml) was heated at 90° for 5 hours. On cooling, the excess of thionyl chloride was removed under reduced pressure and the resulting solid was triturated with hot benzene. Recrystallization from dry acetonitrile gives **4a** as crystalline solid (Table 2). To a solution of the salt **4a** (5 mmoles) in ethanol (50 ml) tetrafluoroboric acid (7 mmoles) was added. The reaction mixture was heated at reflux for 15 minutes. The precipitated solid was collected by filtration and purified by recrystallization to give **4b**.

Acknowledgement.

The authors wish to thank the Comision Asesora de Investigación Científica y Técnica for supporting this research, project number 2019/83.

REFERENCES AND NOTES

- [1] P. Molina, A. Tarraga and C. Martinez, *Synthesis*, 975 (1982); P. Molina, M. Alajarin, A. Arques, R. Benzal and H. Hernandez, *J. Chem. Soc., Perkin Trans. I*, 1891 (1984).
- [2] P. Molina, A. Arques, I. Cartagena and M. V. Valcarcel, *Heterocycles*, **23**, 2357 (1985).
- [3] P. Molina, M. Alajarin and J. R. Saez, *Synthesis*, 983 (1984); P. Molina M. Alajarin, J. R. Saez, M. C. Foces-Foces, F. H. Cano, R. M. Claramunt and J. Elguero, *J. Chem. Soc., Perkin Trans. I*, 2037 (1986).
- [4] P. Molina, M. Alajarin, and M. J. Vilaplana, *Synthesis*, 415 (1983); P. Molina, A. Lorenzo, R. M. Claramunt and J. Elguero, *Tetrahedron Letters*, 5427 (1984); M. Alajarin, P. Molina, A. Tarraga, M. J. Vilaplana, M. C. Foces-Foces, F. H. Cano, R. M. Claramunt and J. Elguero, *Bull. Chem. Soc. Japan*, **58**, 735 (1985).
- [5] P. Molina, M. Alajarin and M. J. Vilaplana, *Heterocycles*, **23**, 641 (1985); M. Alajarin, P. Molina, M. J. Perez de Vega, M. C. Foces-Foces, F. H. Cano, R. M. Claramunt and J. Elguero, *Chem. Scripta*, **25**, 230 (1985).
- [6] P. Molina, M. Alajarin and M. J. Perez de Vega, *Ann. Chem.*, 1540 (1986).
- [7] P. Molina, A. Tarraga and M. J. Lidon, *Synthesis*, 635 (1986).
- [8] P. Molina, A. Tarraga, A. Espinosa and M. J. Lidon, *Synthesis*, 128 (1987).
- [9] Y. Tamura, J. H. Kim and M. Ikeda, *J. Heterocyclic Chem.*, **12**, 107 (1975).
- [10] S. Polanc, B. Vercek, B. Sek, B. Stanovnik and M. Tisler, *J. Org. Chem.*, **39**, 2143 (1974).
- [11] G. M. Bagder, P. J. Nelson and K. T. Potts, *J. Org. Chem.*, **29**, 2542 (1964).
- [12] C. Th. Pedersen and J. Møller, *Tetrahedron*, **30**, 553 (1974).