A Facile Synthesis of Substituted 4,5,6,7-Tetrahydropyrazolo[3,4-*d*]-pyrimidine and 1,2,3,4-Tetrahydropyrazolo[1,5-*a*]triazine Derivatives

J. N. Vishwakarma, M. Mofizuddin, H. Ila* and H. Junjappa*

Department of Chemistry, North-Eastern Hill University,
Shillong 793 003, Meghalaya, India

Received November 3, 1987

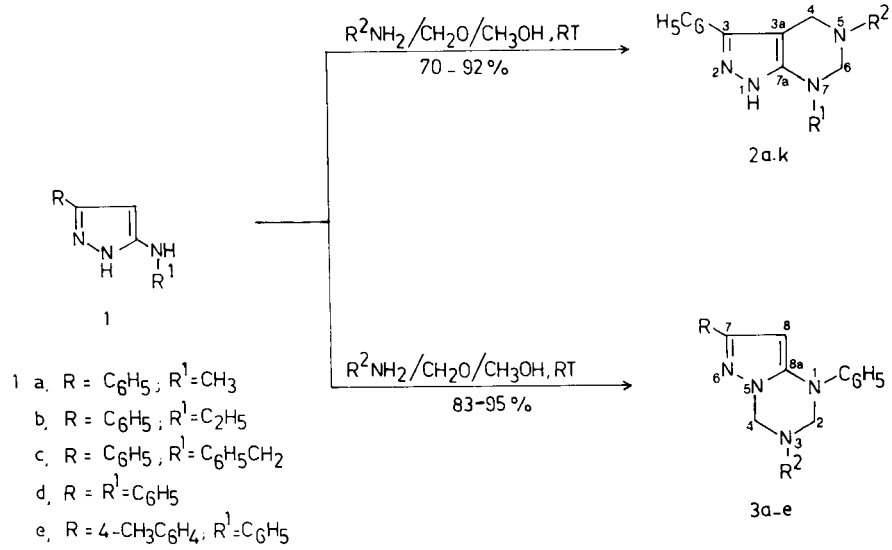
Cyclocondensation of 3(5)-alkylamino- and 3(5)-arylaminopyrazoles **1a-c** and **1d-e** with formaldehyde and primary amines affords novel tetrahydropyrazolo[3,4-*d*]pyrimidines **2** and tetrahydropyrazolo[1,5-*a*]triazine derivatives **3** respectivley in good yields.

J. Heterocyclic Chem., **25**, 1387 (1988).

Several pyrazole[3,4-*d*]pyrimidine derivatives and their mercapto analogs are known to posssess biological activity [1-5], however, the corresponding 4,5,6,7-tetrahydro derivatives have not been investigated for their synthesis and biological activity. Our literature survey at this stage revealed that a few of the 1,3-substituted-5-nitrotetrahydropyrimidines have been reported to be synthesized by cyclocondensation of β-nitroenamines or nitroketene *S,N*-benzylacetals with formaldehyde and primary amines [6-7]. We therefore considered it of interest to employ the previously reported 3(5)-alkyl/arylaminopyrazoles **1** [8] as bifunctional nucleophiles in tetrahydropyrimidine annelation with formaldehyde and amines, which afforded either pyrazolo[3,4-*d*]pyrimidines **2** or pyrazolo[1,5-*a*]triazines **3** in good yields. The results of these studies are reported in this paper.

Results and Discussions.

When **1a**, formaldehyde and benzylamine (1:2:1) were stirred at room temperature in methanol, work-up of the reaction mixture yielded a colorless crystalline solid (90%), which was characterized as 3-phenyl-5-benzyl-7-methyl-4,5,6,7-tetrahydro-1(2*H*)-pyrazolo[3,4-*d*]pyrimidine (**2a**). The reaction was found to be general with other substituted amines (R^2 = CH_3, C_2H_5, C_6H_5) and with the corresponding 3(5)-ethylamino, **1b**, or benzylaminopyrazoles **1c** to give the respective **2b-k** in 70-92% overall yields. However, when the corresponding 3(5)-anilinopyrazole (**1d**) was reacted with benzylamine under identical conditions, the product isolated (92%) was characterized as 1,7-diphenyl-3-benzyl-1,2,3,4-tetrahydropyrazolo[1,5-*a*]triazine (**3a**) instead of the corresponding pyrazolopyrimidine **21** (R^1 = C_6H_5, R^2 = $C_6H_5CH_2$). The triazine **3a** was apparently formed by cyclization on the pyrazole ring nitrogen instead of at C-4 position. The other substituted pyrazolotriazines **3b-e** were similarly obtained from **1d-e** and substituted amines under identical conditions in 83-95% overall yields. The pyrazolotriazines **3** were distinguished from the corresponding pyrazolopyrimidines **2** by the presence



Scheme

Table I

Preparation of 3-Aryl-5,7-alkyl(aryl)-4,5,6,7-tetrahydropyrazolo[3,4-*a*]pyrimidines **2a-k**

Compound	R^1	R^2	Reaction time, hours	Yield %	Mp (°C)	Molecular formula	Analysis (%) Calcd./(Found) C	H	N
2a	CH_3	$C_6H_5CH_2$	10	90	171-172	$C_{19}H_{20}N_4$	74.97 (75.18)	6.62 (6.71)	18.40 (18.68)
2b	CH_3	CH_3CH_2	12	84	140-141	$C_{14}H_{18}N_4$	69.39 (69.11)	7.49 (7.58)	23.12 (23.37)
2c	CH_3	C_6H_5	11	86	164-165	$C_{18}H_{18}N_4$	74.46 (74.76)	6.25 (6.50)	19.29 (19.38)
2d	CH_3	CH_3	12	80	179-180	$C_{13}H_{16}N_4$	68.39 (68.23)	7.06 (7.34)	24.54 (24.66)
2e	C_2H_5	C_2H_5	16	78	159-160	$C_{15}H_{20}N_4$	70.28 (70.47)	7.86 (7.68)	21.85 (22.00)
2f	C_2H_5	$C_6H_5CH_2$	12	90	174-175	$C_{20}H_{22}N_4$	75.44 (75.21)	6.96 (7.03)	17.56 (17.27)
2g	C_2H_5	C_6H_5	20	84	190-191	$C_{19}H_{20}N_4$	74.97 (74.73)	6.62 (6.84)	18.40 (18.68)
2h	C_2H_5	CH_3	12	76	174-175	$C_{14}H_{18}N_4$	69.39 (69.51)	7.49 (7.73)	23.12 (22.91)
2i	$C_6H_5CH_2$	$C_6H_5CH_2$	20	92	198-199	$C_{25}H_{24}N_4$	78.92 (79.17)	6.36 (6.57)	14.72 (14.91)
2j	$C_6H_5CH_2$	CH_3CH_2	12	80	156-157	$C_{20}H_{22}N_4$	75.44 (75.68)	6.96 (7.18)	17.59 (17.73)
2k	$C_6H_5CH_2$	C_6H_5	2	70	170-171	$C_{24}H_{22}N_4$	78.66 (78.89)	6.05 (6.28)	15.29 (15.57)

Table II

Preparation of 7-Aryl-1,3-alkyl(aryl)-1,2,3,4-tetrahydropyrazolo[1,5-*a*]triazines **3a-e**

Compound	R^1	R^2	Reaction time, hours	Yield %	Mp (°C)	Molecular formula	Analysis (%) Calcd./(Found) C	H	N
3a	C_6H_5	$C_6H_5CH_2$	12	92	140-141	$C_{24}H_{22}N_4$	78.66 (78.48)	6.05 (6.27)	15.29 (15.43)
3b	C_6H_5	C_2H_5	16	83	119-120	$C_{19}H_{20}N_4$	74.97 (75.13)	6.62 (6.87)	18.40 (18.66)
3c	C_6H_5	CH_3	20	87	85-86	$C_{18}H_{18}N_4$	74.46 (74.28)	6.25 (6.47)	19.29 (19.41)
3d	C_6H_5	4-$CH_3OC_6H_5$	5	95	152-153	$C_{24}H_{22}N_4O$	75.37 (75.16)	5.80 (6.11)	14.65 (14.48)
3e	4-$CH_3C_6H_4$	C_2H_5	10	94	140-141	$C_{20}H_{22}N_4$	75.44 (75.63)	6.96 (7.21)	17.59 (17.87)

of a signal due to H-8 proton between δ 5.80-6.0 (s, 1H) in their ^{1}H nmr spectra. Besides the band due to ν NH present between 3100-3250 cm^{-1} in the ir spectra of **2a-k** was clearly absent in those of **3a-e** (Table III and IV). The difference in the reactivity of 3(5)-alkylamino, **1a-c**, and the corresponding arylaminopyrazoles **1d-e** to give **2** and **3** respectively can be rationalized in terms of reduced nucleophilicity of C-4 position in **1d** and **1e**, because of increased delocalization of the non-bonding electron pair of the arylamino nitrogen over the aryl group rather than the pyrazole ring, while the nitrogen lone pair in the alkylamino group of **1a-c** is completely delocalized over the pyrazole ring, thus facilitating ring closure at the C-4 position.

The reaction provides a facile entry to hiterto unreported tetrahydropyrazolopyrimidines and tetrahydropyrazolotriazines derivatives.

Table III

Spectral Data for Compounds **2a-k**

Compound	IR (KBr) ν (cm^{-1})	^1H NMR δ (ppm)	MS (70 eV) m/e (%)
2a	3200 (NH), 1590, 1565, 1540	2.80 (s, 3H, NCH_3), 3.90 (s, 2H, NC$H_2C_6H_5$), 3.75 (s, 2H, C-CH_2N), 3.95 (s, 2H, N-CH_2N), 7.00-7.65 (m, 10H, ArH), 9.3 (br s, 1H, NH, exchangeable with deuterium oxide) [a]	304 (M^+, 85), 303 (100), 185 (78), 184 (46)
2b [c]	3150 (NH), 1590, 1560, 1540	1.25 (t, 3H, NCH$_2$CH_3), 2.75 (q, 2H, N-CH_2CH$_3$), 2.82 (s, 3H, NCH_3), 3.80 (s, 2H, C-CH_2N), 3.97 (s, 2H, NCH_2N), 7.20-8.20 (m, 5H, ArH), 9.0 (br s, 1H, NH, exchangeable with deuterium oxide) [a]	242 (M^+, 93), 241 (100), 185 (90), 184 (88)
2c	3150 (NH), 1600, 1540, 1490	3.05 (s, 3H, NCH_3), 4.60 (s, 2H, CCH_2N), 4.80 (s, 2H, NCH_2N), 6.80-8.35 (m, 10H, ArH) [b]	290 (M^+, 66), 289 (41), 185 (100), 184 (60)
2d	3100 (NH), 1590, 1555, 1540	2.40 (s, 3H, NCH_3), 2.73 (s, 3H, NCH_3), 3.70 (s, 2H, C-CH_2N), 3.85 (s, 2H, N-CH_2N), 7.00-7.60 (m, 5H, ArH) [b]	228 (M^+, 89), 227 (87), 185 (90), 184 (88)
2e	3150 (NH), 1590, 1565, 1540	1.10 (t, 3H, CH$_2$CH_3), 1.13 (t, 3H, NCH$_2$CH_3), 2.55 (q, 2H, NCH_2CH$_3$), 3.20 (q, 2H, NCH_2CH$_3$), 3.80 (s, 4H, CCH$_2$N and NCH_2N), 7.00-7.60 (m, 5H, ArH) [b]	256 (M^+, 63), 255 (83), 200 (32), 199 (35), 198 (32), 185 (90)
2f	3200 (NH), 1590, 1563, 1530	1.17 (t, 3H, N-CH$_2$CH_3), 3.30 (q, 2H, NCH_2CH$_3$), 3.80 (s, 2H, N-C$H_2C_6H_5$), 3.93 (s, 2H, C-CH_2N), 4.05 (s, 2H, N-CH_2N), 7.20-7.60 (m, 10H, ArH), 9.30 (br s, 1H, NH, exchangeable with deuterium oxide) [a]	318 (M^+, 69), 317 (100), 200 (60), 199 (61), 198 (60), 185 (69)
2g	3150 (NH), 1600, 1540, 1495	1.10 (t, 3H, NCH$_2$CH_3), 3.24 (q, 2H, NCH_2CH$_3$), 4.40 (s, 2H, CCH_2N), 4.50 (s, 2H, NCH_2N), 6.50-7.75 (m, 10H, ArH) [a]	304 (M^+, 87), 303 (57), 199 (90), 198 (25), 184 (90)
2h	3150 (NH), 1590, 1565, 1540	1.10 (t, 3H, NCH$_2$CH_3), 2.33 (s, 3H, NCH_3), 3.30 (q, 2H, N-CH_2CH$_3$), 3.70 (s, 2H, CCH_2N), 3.75 (s, 2H, NCH_2N), 7.20-7.60 (m, 5H, ArH) [a]	242 (M^+, 85), 241 (72), 199 (54), 198 (36), 184 (100)
2i	3250 (NH), 1590, 1565, 1530	3.70 (s, 2H, C-CH_2N), 3.85 (s, 2H, NC$H_2C_6H_5$), 3.95 (s, 2H, NC$H_2C_6H_5$), 4.40 (s, 2H, NCH_2N), 7.00-7.50 (m, 15H, ArH), 9.10 (br s, 1H, exchangeable with deuterium oxide) [a]	380 (M^+, 50), 379 (66), 261 (31), 260 (47)

Table III (continued)

Compound	IR (KBr) ν (cm^{-1})	^1H NMR δ (ppm)	MS (70 eV) m/e (%)
2j	3225 (NH), 1590, 1560, 1538	0.95 (s, 3H, CH_3CH$_2$), 2.55 (q, 3H, CH$_3$CH_2), 3.70 (s, 2H, CCH_2N), 3.85 (s, 2H, NC$H_2C_6H_5$), 4.33 (s, 2H, NCH_2N), 7.00-7.75 (m, 10H, ArH) [b]	–
2k	3202 (NH), 1598, 1563, 1544	4.35 (s, 4H, CCH_2N and NC$H_2C_6H_5$), 4.45 (s, 2H, NCH_2N), 6.70-7.85 (m, 15H, ArH) [b]	366 (M^+, 70), 365 (49), 261 (68), 260 (100)

[a] In deuteriochloroform. [b] In deuteriodimethyl sulfoxide. [c] ^{13}C NMR (deuteriochloroform): δ 13.14 (*C*H$_3$CH$_2$), 35.74 (*C*H$_3$N), 46.94 (N*C*H$_2$CH$_3$), 47.88 (4-*C*H$_2$), 70.11 (6-*C*H$_2$), 97.68 (*C*-3a), 125.79, 127.68, 128.94 (*C*H, phenyl), 130.45 (*C*-1′ of phenyl), 138.99 (*C*-3), 155.65 (*C*-7a).

Table IV

Spectral Data for Compounds **3a-e**

Compound	IR (KBr) ν (cm^{-1})	^1H NMR δ (ppm) (deuteriochloroform)	MS (70 eV) m/e (%)
3a	1585, 1540, 1500	3.97 (s, 2H, N-C$H_2C_6H_5$), 4.50 (s, 2H, N-CH_2N), 5.10 (s, 2H, NCH_2N), 6.00 (s, 1H, *H*-8), 6.97-7.70 (m, 15H, ArH)	366 (M^+, 44), 247 (100)
3b [a]	1580, 1550, 1500	1.10 (t, 3H, NCH$_2$CH_3), 2.80 (q, 2H, NCH_2CH$_3$), 4.50 (s, 2H, NCH_2N), 5.00 (s, 2H, NCH_2N), 5.90 (s, 1H, H-8), 6.90-7.85 (m, 10H, ArH)	304 (M^+, 36), 247 (100), 246 (97)
3c	1580, 1543, 1500	2.67 (s, 3H, NCH_3), 4.50 (s, 2H, NCH_2N), 5.00 (s, 2H, NCH_2N), 6.00 (s, 1H, H-8), 7.10-7.85 (m, 10H, ArH)	290 (M^+, 22), 247 (72), 246 (78)
3d	1580, 1550, 1510	3.60 (s, 3H, OCH$_3$), 4.95 (s, 2H, NCH_2N), 5.50 (s, 2H, NCH_2N), 5.85 (s, 1H, *H*-8), 6.60-7.82 (m, 14H, ArH)	382 (M^+, 37), 247 (100), 246 (62)
3e	1595, 1580, 1548, 1525, 1495	1.10 (t, 3H, N-CH_2CH$_3$), 2.25 (s, 3H, CH_3), 2.80 (q, 2H, NCH_2CH$_3$), 4.45 (s, 2H, NCH_2N), 4.90 (s, 2H, NCH_2N), 5.80 (s, 1H, *H*-8), 6.90-7.50 (m, 9H, ArH)	318 (M^+, 35), 261 (100), 260 (67)

[a] ^{13}C NMR (deuteriochloroform): δ 13.29 (*C*H$_3$CH$_2$), 45.22 (CH$_3$*C*H$_2$), 66.27, 66.93 (2-*C*H$_2$ and 4-*C*H$_2$), 85.67 (*C*H-8), 120.45, 123.48, 125.33, 127.51, 128.42, 129.42 (*C*H, phenyl), 133.69 (*C*-1′ of 7-phenyl), 144.20, 144.72 (C-7 and C-1′ of *N*-phenyl), 149.90 (*C*-8a).

EXPERIMENTAL

Melting points were determined on Thomas Hoover apparatus and are uncorrected. The reaction mixture were monitored by tlc on silica gel. The ir spectra were recorded on a Perkin Elmer 297 spectrophotometer and the ^{1}H nmr spectra on a Varian EM-390 spectrometer using TMS as the internal standard. The mass spectra were obtained on Jeol D-300 mass spectrometer, while the ^{13}C nmr spectra were obtained on a Brooker WM 400 spectrometer.

Reaction of 3(5)-Alkylamino/arylamino-5(3)-arylpyrazoles **1a-e** with Primary Amines in the Presence of Formaldehyde. Synthesis of **2** and **3**.

General Procedure.

A solution of pyrazole **1** (10 mmoles) in methanol (30 ml) was added to a stirred solution of formaldehyde (20 mmoles, 40% solution) and amines (10 mmoles) in methanol (25 ml) and the reaction mixture was stirred at room temperature for 1-20 hours (monitored by tlc). In a few cases, the products **2** or **3** separated out as colorless solids, which were filtered, washed with methanol (2 x 3 ml), dried and crystallized from chloroform/-hexane to give pure products (Table I and II).

In the case of pyrazolopyrimidines **2b**, **2d**, **2e**, **2h**, **2i** and triazines **3a**, **3b** and **3e**, the solid did not separate out and the reaction mixture and was worked up by removing methanol under reduced pressure. The residue was poured over ice-water (100 ml), extracted with chloroform (2 x 50 ml), dried (sodium sulfate) and chloroform was removed on water bath to give **2** or **3**, which were further purified by crystallization from hexane/chloroform.

Acknowledgement.

We thank U. G. C. New Delhi for financial assistance under COSSIST programme.

REFERENCE AND NOTES

[1] S. Kobayashi, *Chem. Pharm. Bull.*, **21**, 941 (1973).

[2] Y. V. Dobrynin, T. A. Bektemirov, T. P. Ivanova, E. V. Chekunova, O. G. Andzhaparidze, I. A. Korbukh, Y. N. Bulychev. N. G. Yakunina and M. N. Preobrazhenskaya, *Kim.-Farm. Zh.*, **14**, 10 (1980); *Chem. Abstr.*, **93**, 88460d (1980).

[3] B. R. Baker, W. F. Wood and J. A. Kozma, *J. Med. Chem.*, **11**, 661 (1968).

[4] F. Delbarre, C. Auscher, A. Degery, H. Brovilhet, J. L. Oliver, *Presse, Med.*, **76**, 2329 (1968); *Chem. Abstr.*, **70**, 86172n (1969).

[5] J. Riviere, F. M. 5,816; *Chem. Abstr.*, **70**, 118170p (1969).

[6] H. D-Urbanska, A. R. Katritzky, T. Urbansky, *Tetrahedron*, **25**, 1617 (1969).

[7] M. Sone, Y. Tominaga, Y. Matsuda and G. Kobayashi, *Yakugaku Zasshi*, **97**, 262 (1977); *Chem. Abstr.*; **87**, 53195v (1977).

[8] J. N. Vishwakarma, B. K. Roy Chowdhary, H. Ila and H. Junjappa, *Ind. J. Chem.*, **24B**, 472 (1985).