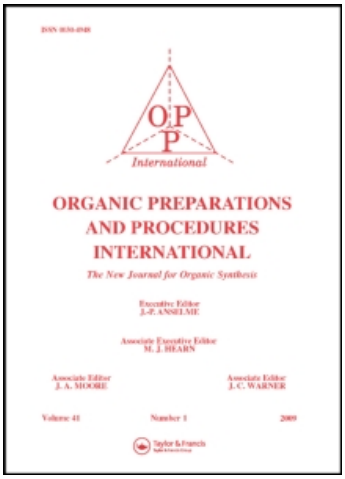


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

AN IMPROVED GENERAL METHOD FOR THE PREPARATION OF 4-ARYL SUBSTITUTED *bis*PYRAZOLO[3,4-b;4,3'-e]PYRIDINES

Agnieszka Puchala[a]; Danuta Rasala[a]; Erkki Kolehmainen[b]; Monika Prokesová[c]
[a] Institute of Chemistry, Pedagogical University, Kielce, POLAND [b] Department of Chemistry, University of Jyväskylä, Jyväskylä, FINLAND [c] Department of Organic Chemistry, Comenius University, Faculty of Natural Sciences, Bratislava, SLOVAKIA

To cite this Article Puchala, Agnieszka , Rasala, Danuta , Kolehmainen, Erkki and Prokesová, Monika(1997) 'AN IMPROVED GENERAL METHOD FOR THE PREPARATION OF 4-ARYL SUBSTITUTED *bis*PYRAZOLO[3,4-b;4,3'-e]PYRIDINES', Organic Preparations and Procedures International, 29: 2, 226 — 230
To link to this Article: DOI: 10.1080/00304949709355191
URL: http://dx.doi.org/10.1080/00304949709355191

9. M. Moreno-Manas and R. Pleixats, *Synthesis*, 430 (1984).

10. L. A. Goding and B. D. West, *J. Org. Chem.*, **33**, 437 (1968).

****

AN IMPROVED GENERAL METHOD FOR THE PREPARATION OF 4-ARYL SUBSTITUTED *bis*PYRAZOLO[3,4-b;4',3'-e]PYRIDINES

Submitted by (03/19/96)

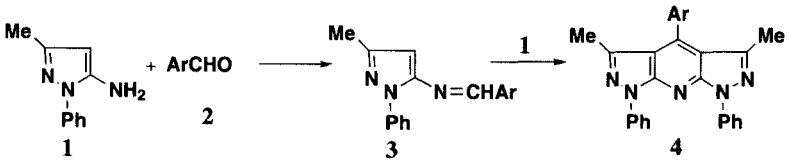
Agnieszka Puchala,[†] Danuta Rasala,[†*] Erkki Kolehmainen[††] and Monika Prokesová[†††]

[†] *Institute of Chemistry, Pedagogical University 5 Checińska Street, PL-25-020 Kielce,POLAND*

[††] *Department of Chemistry, University of Jyväskylä P.O. Box 35, FIN-40351 Jyväskylä, FINLAND*

[†††] *Department of Organic Chemistry, Comenius University, Faculty of Natural Sciences, 84215 Bratislava, SLOVAKIA*

4-Aryl substituted *bis*pyrazolo[3,4-b:4',3'-e]pyridines (BPPs) as large conjugated π-systems are a class of compounds of potential use in photophysical processes such as photo-induced electron transfer reactions.[1] Moreover, a representative number of those derivatives show biological activities.[2] Despite the importance of these compounds, the methodologies available for their preparations are generally limited in scope,[2-7] give poor yields (30-40%) and present problems in purification of the products. The present work describes an improved general procedure for the preparation of a comprehensive series of 4-aryl-3,5-dimethyl-1,7-diphenyl-BPPs.



a) Ar = C_6H_5 **b**) Ar = 4-MeC_6H_4 **c**) Ar = 4-FC_6H_4 **d**) Ar = 4-ClC_6H_4
e) Ar = 4-BrC_6H_4 **f**) Ar = 4-$CF_3C_6H_4$ **g**) Ar = 4-$MeOC_6H_4$ **h**) Ar = 4-$Me_2NC_6H_4$
i) Ar = 4-$NO_2C_6H_4$ **j**) Ar = 4-CNC_6H_4 **k**) Ar = 4-$MeO_2CC_6H_4$ **l**) Ar = 2-BrC_6H_4
m) Ar = 2-furoyl **n**) Ar = 4-pyridyl

In our own experiments, we found ethanol to be a superior solvent to DMF. We also established that the use of a 10% excess of aldehyde led to desired BPPs in much higher yields. An alterna-

tive two-step process (Method B) based on the preparation of Schiff bases (**3**) from 5-amino-3-methyl-1-phenylpyrazole (**1**) and the corresponding aldehyde (**2**) followed by cyclization with **1** was performed. The cyclization to BPPs with or without isolation of the Schiff base proceed highly selectively at 240-250° without solvent for 2 hrs. The overall yields are comparable for both methods (Table 1). All our attempts to use lower temperature (*e.g.* refluxing xylene) as well as prolonged reaction times resulted in lower yields and necessitated tedious chromatographic separations.

TABLE 1. Preparation of 4-Aryl Substituted *bis*pyrazolo[3,4-b;4',3'-e]pyridines (**4**)

No	Method	mp. [°C]	lit. mp. [°C]	Solvent for cryst.	Yield [%]
4a	A	242.5-244	243-244[2] 241-242[6], 240[7]	AcOEt - EtOH (2:1)	73
4b	A	263-266	–	AcOEt - EtOH - CH_2Cl_2 (2:1:2)	71
4c	A	231-232.5	–	AcOEt - EtOH (5:1)	69
4d	A	243.5-244	243[3], 240-241[6]	AcOEt - EtOH (2:1)	62
4e	A	235-237	-	AcOEt - EtOH (2:1)	65
4f	A	254-256	-	AcOEt	74
4g	A	232-233	232[2], 221-222[6]	AcOEt - EtOH (2:1)	54
4h	A	244-246	251-252[2]	AcOEt - EtOH (5:1)	55
4i	B	278.5-281.5	269-271[6]	AcOEt - EtOH - CH_2Cl_2 (1:1:2)	76
4j	B	279-281.5	-	AcOEt - CH_2Cl_2 (1:2)	52
4k	B	269-271	-	AcOEt - CH_2Cl_2 (1:2)	60
4l	A	238-239.5	-	AcOEt - EtOH - CH_2Cl_2 (2:1:3)	64
4m	A	229-231	-	1,4-dioxane	48
4n	B	274	261[3]	AcOEt - EtOH - CH_2Cl_2 (2:1:2)	68

Finally, we find that the electronic properties of the substituent R at the para position of the benzaldehyde are of importance in a selection of the one- or two-step method. Thus, the one-step process is more efficient for electron-donating groups whereas the two-step procedure leads to the high purity BPPs in case of the electron-withdrawing substituent. We believe that the procedure

described here can be utilized for the preparation of other 1,3,4,5,7-pentasubstituted BPPs.

TABLE 2. Elemental Analyses, Mass (MS) and ^{1}H NMR Spectra of 4-Aryl Substituted *bis*Pyrazolo[3,4-b;4',3'-e]pyridines (**4**)

No	Elemental Analyses (Found)			MS M^+(*m/z*) rel. int.(%)	^{1}H NMR (δ, ppm; J, Hz)
	C	H	N		
4a	–	–	–	415 (100)	8.40 (dd, J = 8.2 and 1.1, 4H), 7.51 and 7.55-7.45 (m, 4H), 7.26 (m, 2H), 2.06 (s, 6H)
4b	78.30 (78.50)	5.40 (5.35)	16.30 (16.42)	429 (100)	8.40 (dd, J = 8.2 and 1.1, 4H), 7.51 (m, 4H), 7.33 (s, 4H), 7.26 (m, 2H), 2.49 (s, 3H), 2.08 (s, 6H)
4c	74.81 (74.93)	4.65 (4.49)	16.15 (16.21)	433 (100)	8.39 (dd, J = 8.2 and 1.1, 4H), 7.50 (m, 4H), 7.45 and 7.29 (d, J = 8.7, 2H), 7.24 (m, 2H), 2.08 (s, 6H)
4d	–	–	–	449[a] (100)	8.35 (dd, J = 8.2 and 1.1, 4H), 7.42-7.46 (m, 6H), 7.38 (d, J = 8.6, 2H), 7.26 (m, 2H), 2.03 (s, 6H)
4e	65.60 (65.52)	4.08 (4.29)	14.16 (14.10)	493[b] (94)	8.36 (dd, J = 8.2 and 1.1, 4H), 7.66 and 7.33 (d, J = 8.6, 2H), 7.50 (m, 4H), 7.26 (m,2H), 2.05 (s, 6H)
4f	69.56 (69.67)	4.17 (4.16)	14.48 (14.25)	483 (100)	8.37 (dd, J = 8.2 and 1.1, 4H), 7.81 and 7.61 (dd, J = 8.2 and 0.7, 2H), 7.51 (m, 4H), 7.28 (m, 2H), 2.01 (s, 6H)
4g	75.49 (75.55)	5.20 (5.37)	15.73 (15.89)	445 (100)	8.41 (dd, J = 8.2 and 1.1, 4H), 7.52 (m, 4H), 7.38 and 7.07 (d, J = 8.8, 2H) 7.28 (m, 2H), 3.92 (s, 3H), 2.12 (s, 6H)
4h	75.96 (75.81)	5.72 (5.88)	18.33 (18.18)	458 (100)	8.42 (dd, J = 8.2 and 1.1, 4H), 7.51 (m, 4H), 7.27 and 6.81 (d, J = 8.8, 2H), 7.25 (m, 2H), 3.05 (s, 6H), 2.16 (s, 6H)
4i	70.42 (70.35)	4.38 (4.52)	18.25 (18.32)	460 (100)	8.45 and 7.71(d, J = 8.7, 2H), 8.38(dd, J = 8.2 and 1.1, 4H), 7.54 (m, 4H), 7.30(m, 2H), 2.07(s, 6H)
4k	73.56 (73.37)	4.90 (5.03)	14.79 (14.56)	473 (100)	8.38 (dd, J = 8.2 and 1.1, 4H), 8.24 and 7.65 (d, J = 8.7, 2H), 7.54 (m, 4H), 7.30 (m, 2H), 2.75 (s, 3H), 2.06 (s, 6H)
4l	65.60 (65.73)	4.08 (4.16)	14.16 (14.08)	493[c] (98)	8.42 (dd, J = 8.2 and 1.1, 4H), 7.77 and 7.48 (m, 1H), 7.52 (m, 4H), 7.43-7.42 and 7.27 (m, 2H), 2.08 (s, 6H)
4m	74.07 (74.20)	4.72 (4.78)	17.28 (17.19)	405 (100)	8.42 (dd, J = 8.2 and 1.1, 4H), 7.47 (m, 1H), 7.54 (m, 4H), 7.30 (m, 2H), 6.74 (m, 1H), 6.68 (m, 1H), 2.06 (s, 6H)
4n	74.98 (75.14)	4.84 (4.71)	20.18 (20.32)	416 (100)	8.80 and 7.42 (d, J = 5.5, 2H), 8.35 (d, J = 8.1, 4H), 7.45 (m, 4H), 7.27(m, 2H), 2.02 (s, 6H)

a) *m/z* 450 (35 %) and *m/z* 451 (40 %). b) *m/z* 494 (36 %) and *m/z* 495 (100 %), c) *m/z* 494 (35 %) and *m/z* 495 (100 %).

EXPERIMENTAL SECTION

All melting points were determined on a hot-stage microscope and are uncorrected. Known products were identified by comparison of their melting points and NMR spectra with those of authentic samples available in the literature. For those showing divergent melting points, elemental analyses were carried out. Compounds have been characterised microanalitically and by the molecular ion in their MS spectra as well as ^{1}H NMR measurements. ^{1}H NMR spectra were recorded on a Jeol JNM GSX-270 spectrometer in the FT mode operating at 270.17 MHz for approximately 0.2 M solutions in $CDCl_3$. TMS was used as an internal standard. All low resolution mass spectra were obtained on a Finnigan MAT 95 instrument under electron ionisation (EI) technique by a direct insertion of the sample into the ion source, initially at room temperature, under the following conditions: ionisation energy 70 eV, acceleration potential of electrons 3 kV and source temperature 200°. The mass-to-charge ratio (*m/z*) was verified using perfluorokerosene, C_nF_{2n+2} as a mass-unit standard. The purity of all final compounds was checked by thin-layer chromatography performed on TLC silica gel Merck 60 F_{254} plastic sheets (0.2 mm).

5-Amino-3-methyl-1-phenylpyrazole was obtained according to the procedure given in ref.[8] mp. 114.5-115.5° (lit.[8] mp. 115-116°). Commercially available aldehydes were used as received.

4-Aryl Substituted *bis*Pyrazolo[3,4-b:4',3'-e]pyridines (4). One-Step General Procedure. Method A.- A mixture of 5-amino-3-methyl-1-phenylpyrazole (0.046 mol) and the corresponding aldehyde (0.025 mol) was heated initially at 120-150° until a gas evolution had ceased (usually 30 min) and than for additional 2 hrs at 240-250°. After cooling to room temperature, the resulting solid was refluxed with ethanol for 20 min. The insoluble residue was collected, washed with ethanol and recrystallized from the appropriate solvent system (Table 1).

Preparation of Schiff Bases (3) from 5-Amino-3-methyl-1-phenylpyrazole (1) and Aldehydes (2). - A mixture of 5-amino-3-methyl-1-phenylpyrazole (0.05 mol) and the corresponding aldehyde (0.05 mol) in ethanol (50 mL) was refluxed for 3 hrs. The solvent was evaporated in vacuum and the resulting crude product was recrystallized from ethanol - water (5 : 1) to give a corresponding Schiff base.

(**3i**): yield 85 %, mp. 135.0-136.5° (lit.[8] mp. 134-135°). ^{1}H NMR: δ 8.62 (s, 1H), 8.23 and 7.92 (dd, J = 8.5 and 2.2 Hz, 2H), 7.69 (dd, J = 8.2 and 1.2, 2H), 7.44 (m, 2H), 7.31 (m 1H), 6.23 (s, 1H) and 2.36 (s, 3H).

(**3j**): yield 78 %, mp. 135.5-137.0°. *Anal.* Calcd for $C_{18}H_{14}N_4$: C, 75.50; H, 4.93; N, 19.57. Found; C, 75.39; H, 5.12; N, 19.63. ^{1}H NMR: δ 8.56 (s, 1H), 7.85 (dd, J = 8.1 and 1.7 Hz, 2H), 7.67-7.66 (m, 4H), 7.43 (m, 2H), 7.30 (m, 1H), 6.20 (s, 1H) and 2.35 (s, 3H).

(**3k**): yield 72 %, mp. 86-87°. *Anal.* Calcd for $C_{19}H_{17}N_3O_2$: C, 71.46; H, 5.36; N, 13.16. Found; C, 71.32; H, 5.22; N, 13.24. ^{1}H NMR: δ 8.57 (s, 1H), 8.06 and 7.83 (dd, J = 7.90 and 1.7 Hz, 2H), 7.72 (m, 2H), 7.52 (m, 2H), 7.32 (m, 1H), 6.17 (s, 1H), 3.96 (s, 3H) and 2.35 (s, 3H).

(**3n**): yield 92 %, mp. 83.5-85.0°. *Anal.* Calcd for $C_{16}H_{14}N_4$: C, 73.26; H, 5.38; N, 21.36. Found; C, 73.42; H, 5.22; N, 21.14. ^{1}H NMR: δ 8.32 and 7.68 (d, J = 5.8 Hz, 2H), 8.64 (s, 1H), 7.78 (m, 2H), 7.49 (m, 2H), 7.31 (m, 1H), 6.22 (s, 1H) and 2.36 (s, 3H).

Two-Step General Procedure. Method B.- A mixture of the Schiff base (0.025 mol) and 5-amino-3-methyl-1-phenylpyrazole (0.025 mol) was heated for 2 hrs at 240-250°. For further details see Method A.

Acknowledgements.- We are grateful to the Polish Ministry of Education as well as the Academy of Finland and the University of Jyväskylä for financial support. We also thank to Mr. R. Kauppinen for his help in running the NMR spectra.

REFERENCES

1. K. Rotkiewicz, D. Rasala, A. Puchala, S. Styrcz and T. Bak, Communications presented at: a) *Symposium on Physical Organic Photochemistry*, July 23-27, 1995, Poznañ (Poland); b) *XVIIth International Conference on Photochemistry*, July 30-August 4, 1995, London (UK).

2. K. C. Joshi, K. Dubey and A. Dandia, *Pharmazie*, **36**, 336 (1981).

3. A. Brack, *Ann.*, **681**, 105 (1965).

4. L. R. Swett, J. D. Ratajczyk, C. W. Nordeen and G. H. Aynilian, *J. Heterocycl. Chem.*, **12**, 1137 (1975).

5. E. Gonzales, R. Sarlin and J. Elguero, *Tetrahedron*, **34**, 1175 (1978).

6. L. Hennig, J. Hofmann, M. Alva-Astudillo and G. Mann, *J. prakt. Chem.*, **332**, 351 (1990).

7. L. Hennig, T. Müller and M. Grosche, *ibid.*, **332**, 693 (1990)

8. E. Mohr, *ibid.*, **79**, 1 (1909).

****