Acid-Catalyzed Reaction of Pyrazolo[1,5-*a*]pyridines with Aldehydes: Formation of Bis(pyrazolo[1,5-*a*]pyrid-3-yl)methanes

Yasuyoshi Miki*, Sanae Yagi and Hiroko Hachiken

Faculty of Pharmaceutical Sciences, Kinki University,
3-4-1 Kowakae, Higashi-Osaka 577, Japan

Masazumi Ikeda

Kyoto Pharmaceutical University, Misasagi, Yamashina,
Kyoto 607, Japan

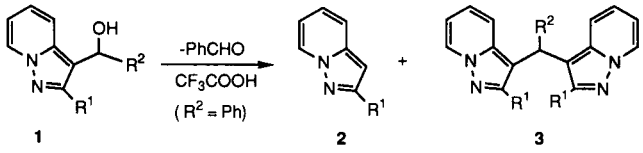
Received January 25, 1993

Reaction of pyrazolo[1,5-*a*]pyridines with aldehydes in the presence of trifluoroacetic acid gave bis(pyrazolo[1,5-*a*]pyrid-3-yl)methanes in high yields.

J. Heterocyclic Chem., **30**, 1045 (1993).

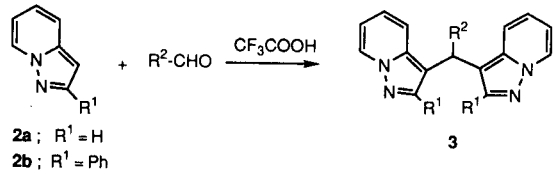
In previous papers [1] [2] we have shown that treatment of 3-(α-hydroxybenzyl)pyrazolo[1,5-*a*]pyridines **1** with trifluoroacetic acid in dichloromethane gives pyrazolo[1,5-*a*]-pyridines **2** and the phenylbis(pyrazolo[1,5-*a*]pyrid-3-yl)-methanes **3** (Scheme 1). The latter product of **3** is assumed to proceed by the acid-catalyzed reaction of **1** with **2** resulting from a retro-aldol-like cleavage of **1**. We were then led to examine the behavior of the pyrazolo[1,5-*a*]-pyridines themselves toward aldehydes under acidic conditions and found that bis(pyrazolo[1,5-*a*]pyrid-3-yl)methanes **3** are formed in high yields.

Scheme 1



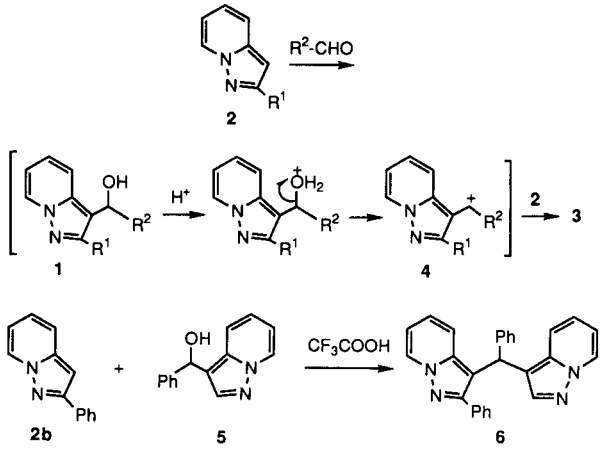
Treatment of pyrazolo[1,5-*a*]pyridine (**2a**) [3] with benzaldehyde in the presence of 2.5 equivalents of trifluoroacetic acid in refluxing dichloromethane for 7 hours gave phenylbis(pyrazolo[1,5-*a*]pyrid-3-yl)methane (**3a**) [1] in 93% yield. Similarly, 2-phenylpyrazolo[1,5-*a*]pyridine (**2b**) [4] reacted with benzaldehyde to afford phenylbis(2-phenylpyrazolo[1,5-*a*]pyrid-3-yl)methane (**3b**) [1] in 99% yield. *p*-Nitro- and *p*-methoxybenzaldehydes were also found to react with **2b** to give the corresponding bis compounds **3c** and **3d** in 77 and 76% yields, respectively. The reaction of formaldehyde and acetaldehyde with **2b** proceeded smoothly even at room temperature to give the bis(pyrazolo[1,5-*a*]pyrid-3-yl)methanes **3e** (83%) and **3f** (68%). These results were summarized in Table 1. The structures of the products were assigned on the basis of the elemental analyses and the spectroscopic evidence (see Experimental). On the other hand, ketones such as cyclohexanone, cyclopentanone, and acetophenone did not react with **2b**.

Scheme 2



A possible mechanism for the formation of **3** is shown in Scheme 3: the initially formed 3-(α-hydroxymethyl)pyrazolo[1,5-*a*]pyridines **1** are converted to the carbenium ion intermediates **4** which combine with **2**. Although the postulated intermediates **1** were not detected at any stage of the reaction, supporting evidence for the proposed mechanism was derived from the reaction of 3-(α-hydroxybenzyl)pyrazolo[1,5-*a*]pyridine (**5**) with 2-phenylpyrazolo-[1,5-*a*]pyridine (**2b**) which gave solely the bis compound **6** in 93% yield. The fact that neither of **3a** nor **3b** were obtained in this reaction clearly indicates that the passage of **1** to **3** is much faster than the reversed reaction of **1** to **2**.

Scheme 3



The present studies have revealed that the pyrazolo[1,5-*a*]pyridines **2** react at the 3-position with aldehydes under

Table 1

Preparation of Bis(pyrazolo[1,5-*a*]pyrid-3-yl)methanes **3**

Compound	R^1	R^2	Condidtions	Yield (%)
3a	H	Ph	reflux, 7 hours	93
3b	Ph	Ph	reflux, 6 hours	99
3c	Ph	*p*-$NO_2C_6H_4$	reflux, 4 hours	77
3d	Ph	*p*-$MeOC_6H_4$	reflux, 13 hours	76
3e	Ph	H	rt, 1 hour	83
3f	Ph	CH_3	rt, 2 hours	68

acidic conditions to form the bis(pyrazolo[1,5-*a*]pyrid-3-yl)-methanes **3** in high yields. We are now examining the reaction of **2** with other electrophiles, in order to explore general and convenient routes to the 3-substituted pyrazolo[1,5-*a*]pyridines.

EXPERIMENTAL

All mps are uncorrected. The ^1H nmr spectra were determined on a JEOL FX200 spectrometer using tetramethylsilane as an internal standard. The ir spectra were recorded with a Hitachi EPI-G2 spectrophotometer. Chromatography was performed on Merck Silica gel (0.040-0.063 mm). Pyrazolo[1,5-*a*]pyridine [3] and 2-phenylpyrazolo[1,5-*a*]pyridine [4] were synthesized by the methods reported.

Reaction of Pyrazolo[1,5-*a*]pyridine (**2a**) or 2-Phenylpyrazolo[1,5-*a*]pyridine (**2b**) with Aldehydes in the Presence of Trifluoroacetic Acid. General Procedure.

To a solution of the pyrazolo[1,5-*a*]pyridines (**2**) (1 mmole) and aromatic aldehydes (1 mmole) or aliphalic aldehydes (3 mmoles) in dichloromethane (10 ml) was added trifluoroacetic acid (2.5 mmoles) and the mixture was stirred at room temperature or refluxed. After the reaction mixture was neutralized with 5% sodium bicarbonate solution, the organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic extracts were washed with water, dried over sodium sulfate, and concentrated. The crude products were purified by column chromatography on silica gel (*n*-hexane/ethyl acetate).

Phenylbis(pyrazolo[1,5-*a*]pyrid-3-yl)methane (**3a**).

Compound **3a** was obtained as an oil [monopicrate mp 187-188° (acetone) (lit [1] mp 187-188°).

Phenylbis(2-phenylpyrazolo[1,5-*a*]pyrid-3-yl)methane (**3b**).

Compound **3b** had mp 125-126° (cyclohexane) (lit [1] mp 125-126°).

p-Nitrophenylbis(2-phenylpyrazolo[1,5-*a*]pyrid-3-yl)methane (**3c**).

Compound **3c** had mp 242-245° (acetonitrile); ^1H nmr (deuteriochloroform): δ 6.18 (s, 1H, CH), 6.52 (dt, 2H, J = 9, 1.5 Hz, 2 x H-4), 6.69 (dt, 2H, J = 7, 1.5 Hz, 2 x H-6), 6.84 (ddd, 2H, J = 9, 7, 1.5 Hz, 2 x H-5), 7.1-7.4 (m, 12H, Ph), 8.10 (d, 2H, J = 9 Hz, *p*-NO_2-Ph), 8.44 (dt, 2H, J = 7, 1.5 Hz, 2 x H-8).

Anal. Calcd. for $C_{33}H_{23}N_5O_2$: C, 75.99; H, 4.44; N, 13.43. Found: C, 75.95; H, 4.46; N, 13.10.

p-Methoxyphenylbis(2-phenylpyrazolo[1,5-*a*]pyrid-3-yl)methane (**3d**).

Compound **3d** had mp 190-191° (methanol); ^1H nmr (deuteriochloroform): δ 3.82 (s, 3H, OCH_3), 6.03 (s, 1H, CH), 6.53 (dt, 2H, J = 9, 1.5 Hz, 2 x H-4), 6.64 (dt, 2H, J = 7, 1.5 Hz, 2 x H-6), 6.78 (ddd, 2H, J = 9, 7, 1.5 Hz, 2 x H-5), 6.82 (d, 2H, J = 9 Hz, *p*-MeO-Ph), 6.8-7.4 (m, 12H, Ph), 8.40 (dt, 2H, J = 7, 1.5 Hz, 2 x H-8).

Anal. Calcd. for $C_{34}H_{26}N_4O$: C, 80.61; H, 5.17; N, 11.06. Found: C, 80.69; H, 5.20; N, 10.95.

Bis(2-phenylpyrazolo[1,5-*a*]pyrid-3-yl)methane (**3e**).

Compound **3e** had mp 169-173° (methanol) (lit [2] mp 169-173°).

1,1-Bis(2-phenylpyrazolo[1,5-*a*]pyrid-3-yl)ethane (**3f**).

Compound **3f** had mp 157-158° (*n*-hexane-benzene); ^1H nmr (deuteriochloroform): δ 1.75 (d, 3H, J = 7.5 Hz, CH_3), 4.93 (q, 1H, J = 7.5 Hz, CH), 6.63 (dt, 2H, J = 7, 1.5 Hz, 2 x H-6), 6.87 (ddd, 2H, J = 9, 7, 1.5 Hz, 2 x H-5), 7.15 (dt, 2H, J = 9, 1.5 Hz, 2 x H-4), 7.25-7.4 (m, 10H, Ph), 8.36 (dt, 2H, J = 7, 1.5 Hz, 2 x H-8).

Anal. Calcd. for $C_{28}H_{22}N_4$: C, 81.13; H, 5.35; N, 13.52. Found: C, 81.22; H, 5.59; N, 13.46.

Phenyl(2-phenylpyrazolo[1,5-*a*]pyrid-3-yl)(pyrazolo[1,5-*a*]pyrid-3-yl)methane (**6**).

To a solution of the 2-phenylpyrazolo[1,5-*a*]pyridine (**2b**) (29 mg, 0.15 mmole) and 3-(α-hydroxybenzyl)pyrazolo[1,5-*a*]pyridine (**5**) [1] (34 mg, 0.15 mmole) in dichloromethane (3 ml) was added trifluoroacetic acid (58 μl, 0.75 mmole) and the mixture was stirred at room temperature for 5 minutes. After the reaction mixture was neutralized with 5% sodium bicarbonate solution, the organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic extracts were washed with water, dried over sodium sulfate, and concentrated. The crude products were purified by column chromatography on silica gel. Elution with *n*-hexane containing gradually increasing amounts of ethyl acetate gave **6** (56 mg, 93%). Compound **6** had mp 197-198° (acetonitrile); ^1H nmr (deuteriochloroform): δ 5.96 (s, 1H, CH), 6.6-7.0 (m, 6H, H-4, H-4', H-5, H-5', H-6 and H-6'), 7.1-7.6 (m, 10H, Ph), 7.51 (s, 1H, H-2), 8.36 (br d, 1H, J = 7 Hz, H-7 or H-7'), 8.41 (br d, 1H, J = 7 Hz, H-7' or H-7).

Anal. Calcd. for $C_{27}H_{20}N_4$: C, 80.98; H, 5.03; N, 13.99. Found: C, 80.98; H, 4.94; N, 13.89.

REFERENCES AND NOTES

[1] Y. Miki, O. Tomii, H. Nakao, M. Kubo, H. Hachiken, S. Takemura and M. Ikeda, *J. Heterocyclic Chem.*, **25**, 327 (1988).

[2] Y. Miki, N. Nakamura, H. Hachiken and S. Takemura, *J. Heterocyclic Chem.*, **26**, 1739 (1989).

[3] V. Boekelheide and N. A. Fedoruk, *J. Org. Chem.*, **33**, 2062 (1968).

[4] Y. Tamura, J.-H. Kim, Y. Miki, H. Hayashi and M. Ikeda, *J. Heterocyclic Chem.*, **12**, 481 (1975).