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One-Step Synthesis of 3,5-Disubstituted-2-pyridylpyrroles from the Condensation of 1,3-Diones and 2-(Aminomethyl)pyridine

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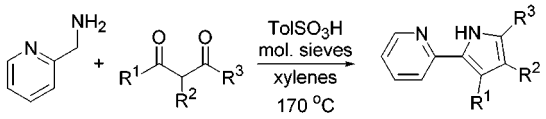
ABSTRACT



3,5-Disubstituted- and 3,4,5-trisubstituted-2-(2-pyridyl)pyrroles may be synthesized efficiently from the novel condensation of 2-(aminomethyl)-pyridine and 1,3-diones. The cyclization reaction was found to proceed through the intermediacy of a (2-pyridyl)methylimine. A marked dependence of the regioselectivity in the reaction of unsymmetrical diones on the presence of additional aminomethylpyridine suggests that two pathways to the product pyrroles are available.

2-(2-Pyridyl)pyrroles are a potentially useful class of compounds. In separate studies, they have been shown to be antioxidants,[1] P38 kinase inhibitors,[2] and prolyl-4-hydroxylase inhibitors.[3] Because of their structural similarity to other α-diimine ligands such as 2,2′-bipyridine, there has also been significant interest in the metal-binding properties of 2-(2-pyridyl)pyrroles.[4−8] There are many synthetic routes to these compounds; however, most of them entail many steps and low yields are normally obtained.[9−16] Through our attempts to prepare bis-*N*-(pyridylmethyl)-1,3-diimines as ligands for transition metal complexation, we have discovered a novel route to pyridylpyrroles involving 2-(aminomethylpyridine) **1** and 1,3-diones.

Heating a xylene solution of **1**, **2**, 0.1 equiv *p*-$CH_3C_6H_4SO_3H$, and molecular sieves at 170 °C for 8 h resulted in conversion to 3,5-dimethyl-2-(2-pyridyl)pyrrole **12** (Scheme 1, Table 1). The reaction was found to be tolerant of a range of R groups with different steric demands, including phenyl, trifluoromethyl, and *tert*-butyl groups (Table 1). Unfortunately, our attempts to perform the reaction of 2-aryl-1,3-dialdehydes resulted in only small amounts of the desired products. The reaction appears to proceed through the

(1) Lehuede, J.; Fauconneau, B.; Barrier, L.; Ourakow, M.; Piriou, A.; Vierfond, J.-M. *Eur. J. Med. Chem.* **1999**, *34*, 991−996.
(2) de Laszlo, S. E.; Visco, D.; Agarwal, L.; Chang, L.; Chin, J.; Croft, G.; Forsyth, A.; Fletcher, D.; Frantz, B.; Hacker, C.; Hanlon, W.; Harper, C.; Kostura, M.; Li, B.; Luell, S.; MacCoss, M.; Mantlo, N.; O'Neill, E. A.; Orevillo, C.; Pang, M.; Parsons, J.; Rolando, A.; Sahly, Y.; Sidler, K.; Widmer, W. R.; O'Keefe, S. J. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2689−2694.
(3) Dowell, R. I.; Hales, N. J.; Tucker, H. *Eur. J. Med. Chem.* **1993**, *28*, 513−516.
(4) Wu, F.; Chamchoumis, C. M.; Thummel, R. P. *Inorg. Chem.* **2000**, *39*, 584−590.
(5) Chiswell, B. *Inorg. Chim. Acta* **1972**, *6*, 629−634.
(6) Jena, S.; Rath, N.; Dash, K. C. *Indian J. Chem., Sect. A: Inorg., Bio-inorg., Phys., Theor. Anal. Chem.* **1999**, *38A*, 350−354.
(7) Perry, C. L.; Weber, J. H. *J. Inorg. Nucl. Chem.* **1971**, *33*, 1031−1039.
(8) Liu, S. F.; Wu, Q.; Schmider, H. L.; Aziz, H.; Hu, N. X.; Popovic, Z.; Wang, S. *J. Am. Chem. Soc.* **2000**, *122*, 3671−3678.
(9) Petrova, O. V.; Mikhaleva, A. I.; Sobenina, L. N.; Shmidt, E. Y.; Kositsina, E. I. *Russ. J. Org. Chem.* **1997**, *33*, 11007-1009.
(10) Firl, J. *Chem. Ber.* **1968**, *101*, 218−225.
(11) Seki, K.; Ohkura, K.; Terashima, M.; Kanaoka, Y. *Heterocycles* **1984**, *22*, 2347−2350.
(12) Savoia, D.; Concialini, V.; Roffia, S.; Tarsi, L. *J. Org. Chem.* **1991**, *56*, 1822−1827.
(13) Bean, G. P. In *Pyrroles: Part 1*; Jones, R. A., Ed.; John Wiley & Sons: New York, 1990; Vol. 48, pp 105−294.
(14) Emmert, B.; Brandl, F. *Chem. Ber.* **1927**, *60*, 2211−2216.
(15) Wibaut, J. P.; Dingemanse, E. *Recl. Trav. Chim.* **1923**, *42*, 1033−1049.
(16) Wibaut, J. P. *Recl. Trav. Chim.* **1926**, *45*, 657−670.

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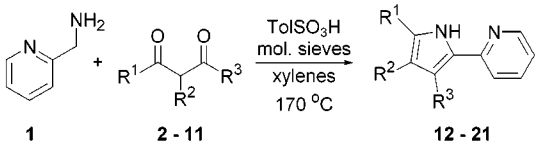
Scheme 1

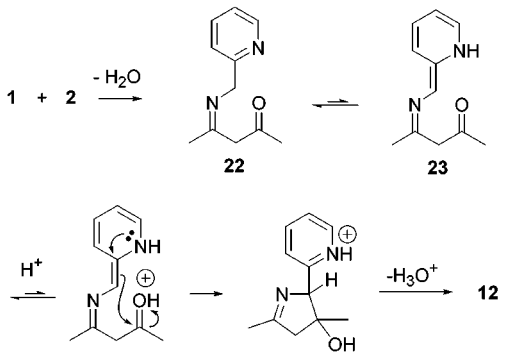


intermediacy of a β-iminoketone, which usually forms readily under ambient conditions. For example, when mixed at room temperature, **1** and **2** gave 4-(2-pyridylmethyl)imino-2-pentanone (**22**) within 10 min as determined by GCMS (Scheme 2).

The cyclization is thought to occur by nucleophilic attack on the ketone carbonyl by the carbon atom α to the pyridine. It is proposed that the nucleophilicity of the (2-pyridyl)methyl carbon arises from the enamine tautomer, **23**. This hypothesis is bolstered by the fact that 4-(aminomethyl)pyridine, which can also tautomerize to an enamine structure, participates in this reaction to give **24**, whereas 3-(aminomethyl)pyridine and benzylamine, which are unable to form enamines, do not participate in the reaction under the same conditions (Scheme 3). This mechanistic proposal is closely related to that put forth for the formation of pyrroles from the reaction of 1,3-diones with 2-aminoesters.[13,17,18] Under the same conditions, the reaction of **1** with unsymmetrically substituted 1,3-diones displays little regioselectivity, although this can be greatly improved by isolation of the intermediate β-iminoketone. The regioselectivity under the one-pot conditions is low although the initial imine formation is usually very selective. For diones **8**, **10**, and **11**, the intermediate β-iminoketone regioisomers are formed in ratios of 85:15, 99.2:0.8, and 94:6, respectively. After heating at 170 °C, the products, **18**, **20**, and **21**, are found in 83:17, 45:55, and 76:25 ratios, respectively. There are notable exceptions to this general rule. For example, when substrate **9**, which contains *tert*-butyl and trifluoromethyl substituents, is treated with **1** only one intermediate imine, resulting from reaction at the CF_3-substituted ketone, and one product, **19**, are observed. Also, the reaction of 4-(aminomethyl)pyridine with substrate **10** is very regioselective, resulting in the formation of the 4-pyridyl analogues of **20a** and **20b** in a 94:6 ratio.

The loss of the regioselectivity with increased heating suggests that the pyrrole formation is under thermodynamic control at 170 °C. However, the situation is somewhat more

Scheme 2. Proposed Involvement of the Enamine Tautomer **23** in the Cyclization Reaction



Scheme 3

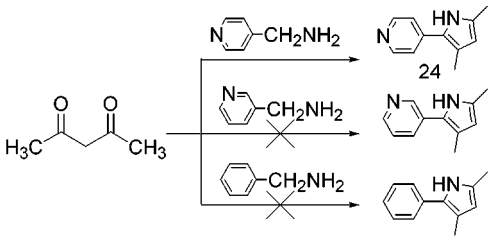


Table 1. Products Obtained from the Condensation of 2-(Aminomethyl)pyridine (**1**) and Various 1,3-Diones

entry	dione	pyrrole product(s)	isol. % yld
1	**2**, R = H	**12**	74
2	**3**, R = Me	**13**	55
3	**4**, R = Et	**14**	41
4	**5**, R = H	**15**	69
5	**6**, R = Me	**16**	52
6	**7**	**17**	50
7	**8**	**18a**, **18b**	47[a]
8	**9**	**19**	64
9	**10**	**20a**, **20b**	98[a](7.4, 2.8)
10	**11**	**21a**, **21b**	12, 37

[a] Isolated as a mixture of regioisomers.

(17) Mataka, S.; Takahashi, K.; Tsuda, Y.; Tashiro, M. *Synthesis* **1982**, *2*, 157−159.
(18) Paine, J. B., III; Dolphin, D. *J. Org. Chem.* **1985**, *50*, 5598−5604.

complicated. If the reaction were truly under thermodynamic control, then submitting one of the regioisomeric products to the reaction conditions should produce a mixture of both regioisomers. When **20a** is heated to 170 °C in the presence of tosic acid and **1**, no interconversion with **20b** is observed.

Further evidence against thermodynamic control of the reaction comes from the dependence of the regioisomeric ratio on the amount of 2-(aminomethyl)pyridine, **1**, present. When **25a**, isolated and purified by vacuum distillation, is heated with a catalytic amount of tosic acid, primarily one product regioisomer, **20a**, is formed. Performing the same reaction with increased amounts of **1** leads to increased production of the opposite regioisomer, **20b** (Table 2).

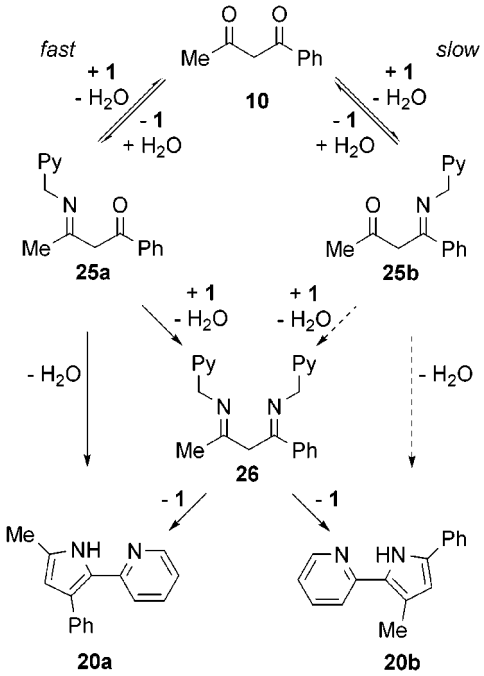
Table 2. Effect of Added **1** on the Regioselectivity of the Conversion of β-Iminoketone **25a** to **20a** and **20b**

		regioisomeric ratio	
entry	equiv of **1**	**20a**	**20b**
1	0.0	90	10
2	0.25	85	15
3	0.52	79	21
4	0.76	76	24
5	1.0	64	36

The role that **1** performs in facilitating the formation of both regioisomers of the product is not fulfilled by close structural mimics. Because pyridine and benzylamine contain the same functional groups in isolation that 2-(aminomethyl)-pyridine has in concert, the cyclization of **25a** to pyrrole products was performed in the presence of these compounds. When **25a** is heated in the presence of pyridine as well as the tosic acid catalyst and molecular sieves, conversion to **20a** is observed. When **25a** is heated similarly with benzylamine, imine metathesis is observed, in which the 2-(aminomethyl)pyridine group is replaced by benzylamine.

These results lead to a mechanistic proposal that contains two pathways for the formation of products from the β-iminoketone intermediate, **25a** (Scheme 4). The first pathway involves nucleophilic attack of the ketone carbonyl by the aminomethyl carbon, as described above. This pathway would lead to only one regioisomeric product, **20a**. The second pathway involves the condensation of a second equivalent of **1** with **25a** to form β-diimine, **26**. Intermediate **26** is capable of cyclizing two ways, leading to both regioisomeric products. The conversion of **25a** to **20a** and

Scheme 4. Proposed Mechanism for Formation of **20a** and **20b**



20b via the second pathway is therefore catalytic in **1**. Presumably there is an analogous set of pathways leading from **25b** to **20a** and **20b** (the dashed arrows in Scheme 4), but these are believed to be much less important and are not needed to explain the results obtained. From a practical synthetic standpoint, these results indicate that the regioselectivity of the reaction with unsymmetrical diones can be greatly enhanced by isolation of the intermediate β-iminoketone and performing the cyclization in the absence of **1**.

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Supporting Information Available: Detailed descriptions of experimental procedures and spectroscopic and analytical data are available for compounds **6**, **12**−**25a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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