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Highly Regioselective Friedländer Reaction

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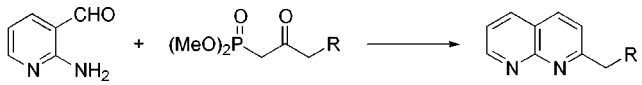
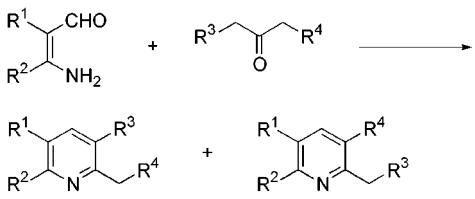
ABSTRACT



A highly regioselective Friedländer reaction is described. By introduction of a phosphonate group at one of the α-carbons of a ketone, regioselectivity can be perfectly controlled.

In connection with our research interests, we needed a general method to prepare 2-substituted [1,8]naphthyridines. There are two general methods for making naphthyridines, namely, the Skraup reaction and the Friedländer reaction. The former is a powerful method for the syntheses of quinolines and many naphthyridines.[1] However, it is very substrate dependent and has not been suitable for the preparation of 2-substituted [1,8]naphthyridines.[2] On the other hand, the Friedländer reaction is one of the most important methods for synthesizing pyridines, quinolines, and naphthyridines.[3] This method typically provides products with high yields, but one of the major drawbacks is that unsymmetrical ketones give both regioisomeric products, generally with little or no selectivity (Scheme 1). Although

Scheme 1. Friedländer Reaction



this reaction was discovered more than a century ago, this regioselectivity problem has never been effectively addressed. For this reason, application of the Friedländer reaction has been limited. In fact, only β-ketoesters and 1,3-diketones undergo the Friedländer reaction regioselectively to provide 2,3-disubstituted pyridines and their derivatives with excellent yields.[4]

Herein, we report a novel, highly regioselective Friedländer reaction leading to 2-substituted [1,8]naphthyridines in high yield. This new method should be applicable not only to naphthyridines but also to other heterocycles such as quinolines.

Our initial approach to controlling regioselectivity was to differentiate the two α-positions of a ketone by regioselective enolate formation. Exploratory work along these lines focused on use of Lewis acids such as $TiCl_4$ to form terminal enols of methyl ketones, so that the Friedländer reaction would occur at the terminal (methyl) position. Unfortunately, even though some increase in regioselectivity was observed, it remained very low.

To differentiate between the two α-carbons of ketones, we decided to introduce at one of the α-positions of the ketone an acidifying directing group, which was not only a good electron-withdrawing group but also a good leaving group. A phosphonate group was chosen since it should serve

(1) For a review, see: Hamada, Y.; Takeuchi, I. *Yakugaku Zasshi* **2000**, *120*, 206.

(2) Hamada, Y.; Takeuchi, I. *Chem. Pharm. Bull.* **1971**, *19*, 1857.

(3) For the newest review, see: Cheng, C.-C.; Yan, S.-J. In *The Friedländer Synthesis of Quinolines*; Dauben, W. C., Ed.; Organic Reactions; J. Wiley & Sons: New York, 1982; Vol. 28, p 37.

(4) (a) Breitmaier, E.; Bayer, E. *Tetrahedron* **1970**, *26*, 5907. (b) Veronese, A. C.; Callegari, R.; Salah, S. A. A. *Tetrahedron Lett.* **1990**, *31*, 3485. (c) Veronese, A. C.; Callegari, R.; Morelli, C. F. *Tetrahedron* **1995**, *51*, 12277.

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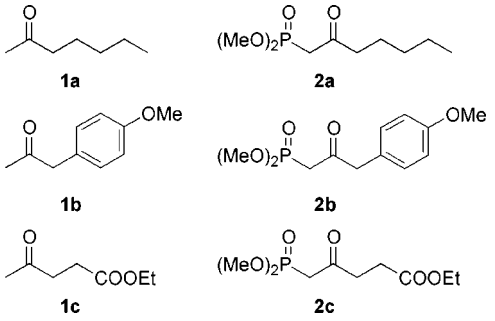
both functions. We envisioned that the α-carbon of the phosphonate would react with the aldehyde selectively, and therefore, the reaction with β-keto phosphonates[5] would provide the desired 2-substituted [1.8]naphthyridines as the sole regioisomer. To test this hypothesis, β-keto phosphonates **2a**,[6] **2b**,[7] and **2c**[8] were chosen as substrates. The Friedländer reaction with 2-amino-3-formylpyridine (**3**)[9] was carried out in MeOH in the presence of aqueous NaOH at room temperature. For comparison, the corresponding methyl ketones (**1a**, **1b**, and **1c**) were also examined (Scheme 2).

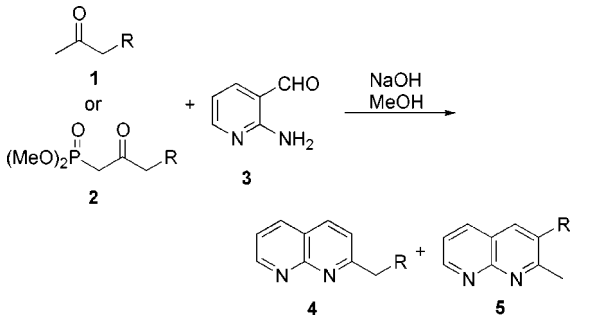
Scheme 2. Ketones and β-Keto Phosphonates



In the case of methylketones, the Friedländer reactions gave naphthyridines with low regioselectivity, and the ratio of **4**:**5** ranged from 67:33 to 13:87. In strong contrast to methyl ketones, all three Friedländer reactions using β-keto phosphonates resulted in single regioisomers **4** with excellent isolated yields (Table 1). Of particular note, for the 4-methoxyphenylacetone example, the regioselectivity was dramatically reversed from 13:87 to 100:0 (entries 3 and 4).

In this newly developed Friedländer reaction, an intermediate was typically observed by HPLC analysis. As the reaction progressed, the intermediate grew in and then was converted to the product. All attempts to isolate the intermediate failed under the standard reaction conditions. However, we were able to stop the reaction at the intermediate stage by using THF as solvent instead of methanol. Thus, the intermediate was isolated and identified as the *trans*-Horner−Emmons product **7**. The desired 2-substituted [1.8]-naphthyridine was smoothly obtained when **7** was subjected to the original reaction conditions (aqueous NaOH in MeOH).

Table 1. Friedländer Reaction

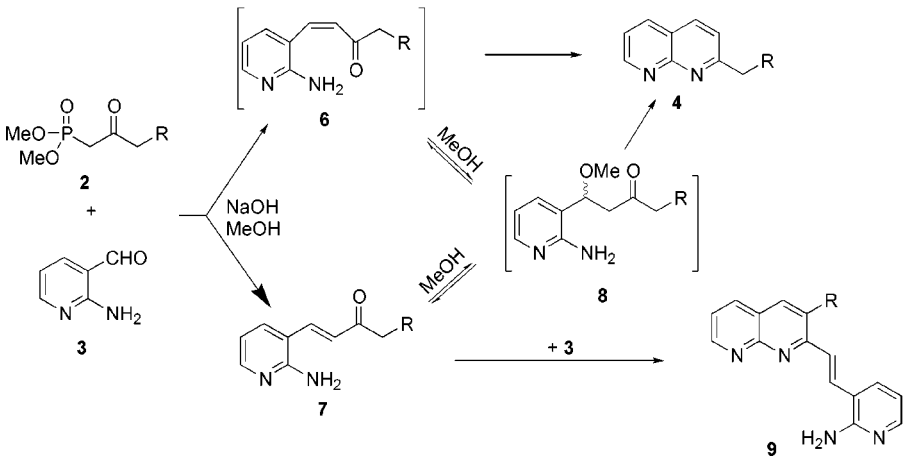


entry	substrate	yield, %	selectivity **4**:**5**
1	**1a**	91	64:36
2	**2a**	95	100:0
3	**1b**	94	13:87
4	**2b**	90	100:0
5	**1c**	89	67:33
6	**2c**	85	100:0

All reactions were carried out in MeOH and NaOH at room temperature.[10] Reaction yields and selectivities were determined by NMR with mesitylene as internal standard.

On the basis of these observations, we believe that the Friedländer reaction of β-keto phosphonates occurs via the *trans*-Horner−Emmons intermediate. More importantly, the *cis*−*trans* isomerization of **7** is promoted by methanol, possibly through the methanol adduct **8**. Either the *cis* compound **6** or the adduct **8** can undergo cyclization and subsequent aromatization to give the desired product **4** (Scheme 3). It is also worth mentioning that slow addition of 2-amino-3-formylpyridine (**3**) provided better results by

Scheme 3. Reaction Mechanism



preventing the second Friedländer reaction between the intermediate **7** and **3** to give compound **9**.

In conclusion, we have discovered a new method for obtaining perfect control of regioselectivity in the Friedländer reaction by attaching a phosphonate activating group at one of the α-carbons of a ketone. To the best of our knowledge, this is the first example using a *β*-keto phosphonate for the Friedländer reaction. The reaction proceeds through the *trans* Horner−Emmons intermediate **7**, and methanol is likely involved in the *cis*−*trans* isomerization, which is critical for this reaction.

Acknowledgment. We thank Drs. M. S. Jensen, M. Palucki, D. R. Gauthier, and M. E. Duggan for helpful discussions and Mr. R. A. Reamer and Ms. L. M. DiMichele for NMR support.

Supporting Information Available: Characterization data for compounds **4** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL006785V

(5) Corey, E. J.; Kwiatkowski, G. T. *J. Am. Chem. Soc*. **1966**, *88*, 5654.

(6) Commercially available from Aldrich.

(7) The synthesis of **2b** followed a standard procedure: (a) Kanemasa, S.; Otsuka, T.; Doi, K.; Tsuge, O.; Wada, E. *Synthesis* **1990**, 1167. (b) Shapiro, G.; Buechler, D.; Hennet, S. *Tetrahedron Lett.* **1990**, *31*, 5733. ^{1}H NMR ($CDCl_3$) δ 7.12 (m, 2H), 6.86 (m, 2H), 3.82 (s, 2H), 3.79 (s, 3H), 3.78 (d, J = 11.1 Hz, 6H), 3.09 (d, J = 22.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 199.4 (d, J_{CP} = 6.1 Hz), 158.5, 130.3, 125.1, 113.8, 54.8, 52.5 (d, J_{CP} = 6.4 Hz), 49.4 (d, J_{CP} = 1.2 Hz), 39.6 (d, J_{CP} = 128.3 Hz).

(8) Delamarche, I.; Mosset, P. *J. Org. Chem*. **1994**, *59*, 5453.

(9) Rivera, N. R.; Hsiao, Y.; McWilliams, C.; Cowen, J. A.; Armstrong, J.; Yasuda, N.; Hughes, D. L. *Synth. Commun*. In press.

(10) **Typical Experimental Procedure.** Into a methanol solution of the *β*-keto phosphonate (1.1 equiv, concentration 0.44 M) was added 2-amino-3-formylpyridine (0.8 equiv). Aqueous NaOH (1.2 equiv, 50 wt %) was then added slowly over a 10 min period such that $T_{max} \leq 41$ °C. The solution was stirred for 30 min, after which the remainder of the aldehyde (0.2 equiv) was added over 3 min. The reaction was allowed to stir overnight at room temperature (20 °C). The crude mixture was concentrated, and the residue was dissolved in EtOAc. After a water wash, the organic solution was concentrated to give the desired naphthyridine product.