Tetrahedron Letters,Vol.27,No.33,pp 3865-3868,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

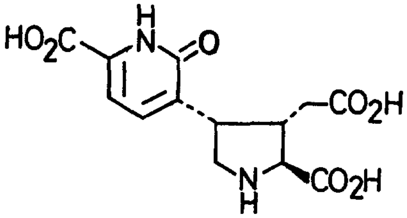
A NEW PYRIDINE SYNTHESIS STARTING FROM α, β-UNSATURATED CARBONYL COMPOUNDS

Katsuhiro Konno, Kimiko Hashimoto, Haruhisa Shirahama
and Takeshi Matsumoto
Department of Chemistry, Faculty of Science, Hokkaido University,
Sapporo 060, Japan

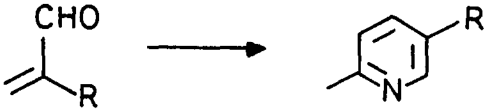
Abstract —— A new and mild synthetic method of substituted pyridines from α, β-unsaturated carbonyl compounds through a sequence involing (1) 1, 4-conjugate addition of thiophenol (2) condensation with a methylene ketone (3) Pummerer rearrangement to an unsaturated 1, 5-dicarbonyl compound (4) treatment with ammonia is described.

Aromatic ring formation from nonaromatic precursor, aromatic annelation, is of renewed interest in the field of pyridine synthesis[1] as well as phenol synthesis.[2] For complex natural product synthesis containing these moieties, however, it still remained to be of limited use.

In the course of synthetic studies on acromelic acid A , a neurotoxin from a poisonous mushroom[3], we needed to construct a 2,5-disubstituted pyridine ring from an α-substituted α, β-unsaturated aldehyde. Our efforts to solve this problem resulted in a mild and versatile method of pyridine synthesis.[4]

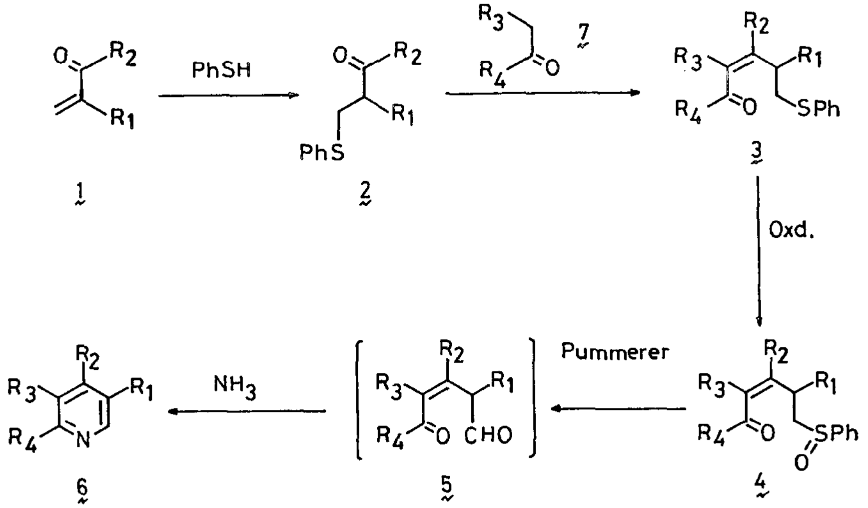


acromelic acid A



Cyclization of unsaturated 1, 5-dicarbonyl compounds with a variety of ammonia sources is a facile process for pyridine formation.[5] However, difficluties encountered in preparation of unsaturated 1,5-dicarbonyl compounds made it of limited use in synthesis. In our method the problem was solved by the use of the Pummerer reaction.[6]

Scheme 1.

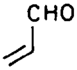
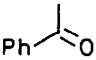
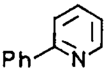
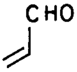
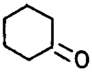
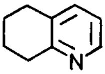
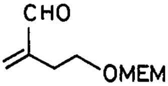
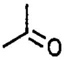
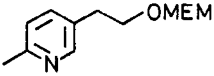
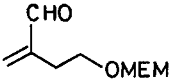
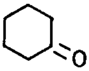
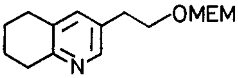
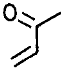
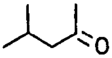
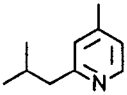
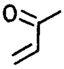
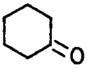
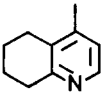
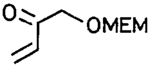
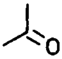
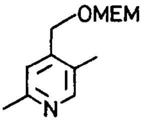


As shown in Scheme 1, an α, β-unsaturated ketone bearing phenylthio group at δ-position such as 3 can be regarded as a synthetic equivalent to ketoaldehyde 5 since the phenylthiomethyl group may be convertible to aldehyde by the Pummerer reaction. Moreover, ketosulfide 3 is expected to be readily accessible because the reaction sequence 1→2→3 is a feasible and conventional process.

The results are summarized in Table 1. Typical example is as follows (entry 5): Treatment of methyl vinyl ketone (1: R_1 = H, R_2 = Me) with thiophenol and triethylamine (1.2 equiv each) in THF at 0 °C for 30 min afforded adduct 2 in 98 % yield, which was condensed with methyl isobutyl ketone (7: R_3 = H, R_4 =iBu, 2 equiv) by treatment with LDA/THF-HMPA at -78 °C for 15 min, and then dehydrated by $SOCl_2$ (2 equiv)-DMAP (4 equiv) in CH_2Cl_2 at 0 °C for 15 min to give ketosulfide 3 in 82 % yield. The crude sulfoxide obtained from 3 (1.2 equiv $NaIO_4/H_2O$-MeOH, rt, 2h) was treated with 10 equiv trifluoroacetic anhydride and 25 equiv pyridine in CH_2Cl_2 at 0 °C for 20 min to afford a rearranged product, which was immediately cyclized, in one-pot operation, with methanolic ammonia at 0°→rt for 16h. Thus, 2-isobutyl-4-methylpyridine was obtained in 80% yield.

The yields were usually high in each step and the reactions proceeded under quite mild conditions. Especially, the highly mild and accelerative conditions of the Pummerer reaction is noteworthy.[7)] Pyridines with a variety of substitution pattern could be prepared by a variety of combination of the starting unsaturated carbonyl compounds and ketones. In addition, ready availability of the two components makes this method advantageous.[8)]

Table 1.

	starting material	ketone	pyridine[a]	yield(%)[b]
1				49
2				58
3				52
4				55
5				60
6				60
7				51

a. Spectral data (^{1}H NMR, IR, UV and HR-MS) of these compounds were consistent with the assigned structures or those reported in literature.

b. Isolated overall yield of pyridines.

References and Notes

1) (a) M. A. Tius, A. Thurkauf and J. W. Truesdell, *Tetrahedron Letters*, **23**, 2819 (1982), (b) K. T. Potts, M. J. Cipullo, P. Ralli and G. Theodoridis, *J. Org. Chem.*, **47**, 3027 (1982).

2) (a) D. L. Boger and M. D. Mullican, *J. Org. Chem.*, **45**, 5002 (1980), (b) M. A. Tius, A. Thurkauf and J. W. Truesdell, *Tetrahedron Letters*, **23**, 2823 (1982), (c) M. A. Tius and S. Ali, *J. Org. Chem.*, **47**, 3163 (1982).

3) K. Konno, H. Shirahama and T. Matsumoto, *Tetrahedron Letters*, **24**, 939 (1983).

4) A part of this work was presented at the 17th Congress of Heterocyclic Chemistry, in Sapporo, Japan, August 28, 1985, Abstr., p. 133.

5) (a) E. Klinsberg, "The Chemistry of Heterocyclic Compounds. Pyridine and Its Derivatives", Interscience, New York (1960), (b) R. A. Abramovitch, "The Chemistry of Heterocyclic Compounds. Supplemet of Pyridine and Its Derivatives." Wiley-Interscience, New York (1974).

6) For applications of the Pummerer reaction to natural product synthesis, see: (a) T. Matsumoto, H. Shirahama, A. Ichihara, H. Shin, S. Kagawa, F. Sakan, S. Matsumoto and S. Nishida, *J. Am. Chem. Soc.*, **90**, 3280 (1968). (b) P. Magnus, T. Gallagher, P. Brown and J. C. Huffman, *J. Am. Chem. Soc.*, **106**, 2105 (1984). (c) T. Ikeda and C. R. Hutchinson, *J. Org. Chem.*, **49**, 2837 (1984).

7) In our laboratory, a various acceleration conditions for the Pummerer reaction by using pyridine as additive to acetic anhydride were studied in the cource of the total syntheses of illudin S and M; T. Matsumoto, H. Shirahama, F. Sakan and K. Takigawa, *Bull. Chem. Soc. Jpn.*, **50**, 325 (1977).

8) The utility of this method in natural product synthesis has already been demonstrated by the synthesis of acromelic acid A; K. Konno, K. Hashimoto, Y. Ohfune, H. Shirahama and T. Matsumoto, *Tetrahedron Lett.*, **27**, 607 (1986).

(Received in Japan 26 April 1986)