STUDIES ON as-TRIAZINE DERIVATIVES XIII[1]

A FACILE SYNTHESIS OF FUSARIC ACID FROM THIENYL-as-TRIAZINE DERIVATIVE

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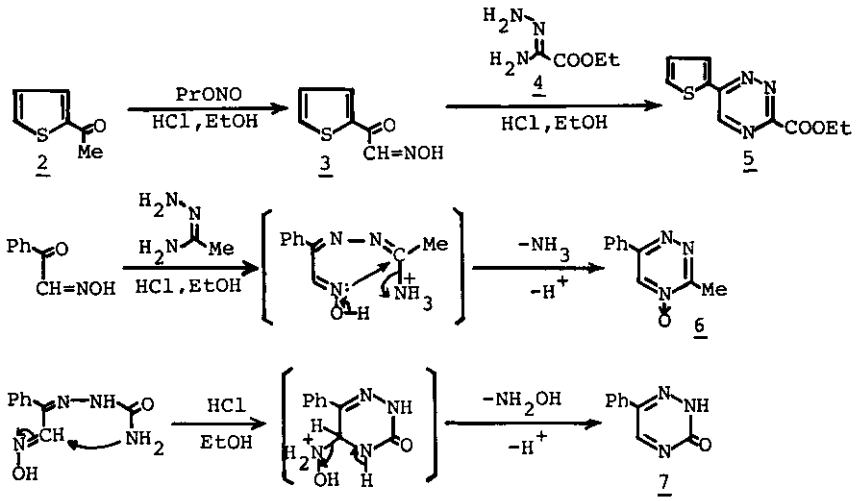
Abstract —— Reverse electron-demand Diels-Alder reaction of ethyl 6-(2-thienyl)-1,2,4-triazine-3-carboxylate with norbornadiene in boiling p-xylene followed by the elimination of cyclopentadiene (retro Diels-Alder reaction) gave 5-(2-thienyl)pyridine-2-carboxylate. Desulfurization of the thienylpyridine with Raney nickel and subsequent saponification afforded fusaric acid (5-butylpyridine-2-carboxylic acid).

Fusaric acid (5-butylpyridine-2-carboxylic acid) (**1**) produced by Fusarium oxysporum is known to be a potent inhibitor for dopamine β-hydroxylase.[2] From the pharmaceutical point of view, the synthesis of **1** has been reported by several investigators,[3] but most of these works consisted of multi-step reaction sequence in spite of rather simple structure of the target compound (**1**). In the present paper, the authors describe a short step synthesis of **1**, using reverse electron-demand Diels-Alder type reaction[4] of ethyl 6-(2-thienyl)-1,2,4-triazine-3-carboxylate (**5**) with norbornadiene (**6**).

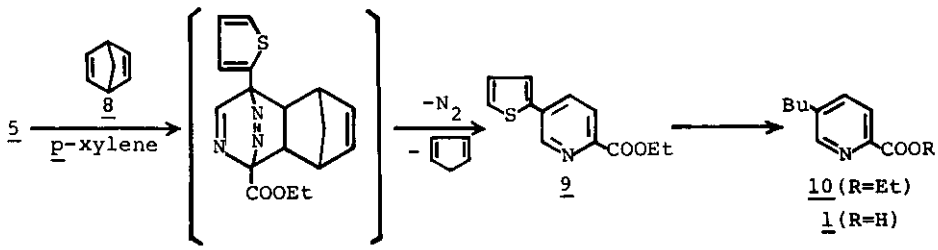
When 2-acetylthiophene (**2**) was treated with propyl nitrite in ethanolic hydrogen chloride , 2-thienylglyoxal aldoxime (**3**), mp 112-114°C [lit.[5] mp 110-114°C] was obtained in 47 % yield. The condensation of **3** with ethoxycarbonylformamidrazone (**4**)[6] in ethanolic hydrogen chloride afforded ethyl 6-(2-thienyl)-1,2,4-triazine-3-carboxylate (**5**), mp 176-177°C, in 46% yield. In connection with this cyclization, Neunhoeffer et al.[7] reported that phenylglyoxal aldoxime reacted with acetamidrazone in acidic medium to give 3-methyl-6-phenyl-1,2,4-triazine

4-oxide (**6**), and Lalezari et al.[8] described phenylglyoxal aldoxime semicarbazone being converted into 6-phenyl-2,3-dihydro-1,2,4-triazin-3-one (**7**), which are illustrated in Scheme 1. In the case of **3**, the cyclization proceeded according to the Lalezari type direction, and **5** was obtained as a sole product, although the reason is obscure at present.



Scheme 1

When **5** was heated with norbornadiene (**8**) in p-xylene under reflux for 5.5 h, ethyl 5-(2-thienyl)pyridine-2-carboxylate (**9**), mp 65-67°C [^{1}H-nmr(CCl_4) δ : 1.43(3H,t,J=7Hz), 4.36(2H,q,J=7Hz), 6.9-7.2(1H,m), 7.2-7.5(2H,m), 7.7-8.2(2H,m), 8.7-9.0(1H,m). Ir ($CHCl_3$)cm^{-1}: 1720] was isolated in 61% yield.[9] Desulfurization of **9** with Raney nickel under conventional conditions gave ethyl 5-butylpyridine-2-carboxylate (**10**) in 48% yield.

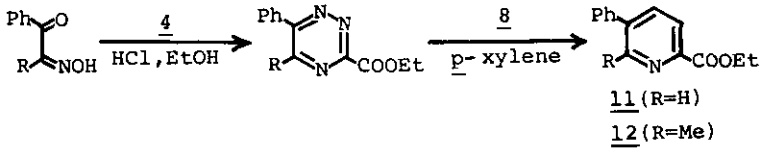


Scheme 2

The spectral data [^{1}H-nmr(CCl_4) δ : 0.93(3H,t,J=7Hz), 1.43(3H,t,J=7Hz), 1.0-2.0 (4H,m), 2.66(2H,t,J=7Hz), 4.36(2H,q,J=7Hz), 7.50(1H,dd,J=2Hz,J=8Hz), 7.93(1H,d,

J=8Hz), 8.43(1H,d,J=2Hz). Ir ($CHCl_3$)cm^{-1}: 1740] of **10** were satisfactory to the desired structure, and the subsequent saponification of **10** with ethanolic sodium hydroxide yielded fusaric acid (**1**), mp 98-100°C, which was identical with an authentic specimen[10] in all respect.

In addition to the above investigation, ethyl 5-phenylpyridine-2-carboxylate (**11**) (81%) and ethyl 6-methyl-5-phenylpyridine-2-carboxylate (**12**) (76%) were easily synthesized by the condensation of the corresponding monoxime of α-dicarbonyl compounds with **4** followed by the Diels-Alder type ring-transformation, as shown below.



11(R=H)
12(R=Me)

Scheme 3

Based on these results, the reaction of 6-substituted 1,2,4-triazine-3-carboxylates with norbornadiene appears to have generality to certain degree for the synthesis of 5-substituted picolinic acids.

ACKNOWLEDGEMENT

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REFERENCES AND NOTES

1. Part XII: S. Konno, M. Sagi, E. Takaharu, S. Fujimura, K. Hayashi, and H. Yamanaka, Chem. Pharm. Bull., 1988, **36**, 1721.
2. H. Umezawa, T. Takeuchi, K. Miyano, T. Koshigoe, and H. Hamano, J. Antibiot. (Totyo), Ser. A, 1973, **26**, 189; Y. Ishii, Y. Fujii, C. Miura, and H. Umezawa, Arzeim.-Forsch., 1975, **25**, 55.
3. Pl. A. Plattner, W. Keller, and A. Boller, Helv. Chim. Acta, 1954, **37**, 1379; T. Nakashima, Yakugaku Zasshi, 1955, **75**, 1012; E. Hardegger and E. Nikles, Helv. Chim. Acta, 1957, **40**, 1016; K. Schreiver and G. Adam, Chem. Ber., 1960, **93**, 1848; Yu. I. Chumakov and V. P. Sherstyuk, Tetrahedron Lett., **1966**, 5887; A. N. Kost, P. B. Terentev, and L. V. Moshentseva, J. Indian Chem. Soc., 1968, **45**, 1109; E. Langhals, H. Langhals, and C. Rüchardt, Justus Liebigs Ann. Chem., **1982**, 930.

4. D. L. Boger, Tetrahedron, 1983, **39**, 2869; H. Neunhoeffer, "Comprehensive Heterocyclic Chemistry", Vol.3, ed. by A. Katritzky, Pergamon Press, New York, **1984**, p.385.
5. G. Barger and A. P. T. Easson, J. Chem. Soc., **1938**, 2100.
6. P. Schmidt and J. Druey, Helv. Chim. Acta, 1955, **38**, 1560.
7. H. Neunhoeffer, F. Weischedel, and V. Böhnisch, Justus Liebigs Ann. Chem., 1971, **750**, 12.
8. L. Lalezari, N. Sharghi, A. Shafiee, and M. Yalpani, J. Heterocycl. Chem., 1966, **6**, 403.
9. Elix et al. reported that the reaction of ethyl 5,6-diphenyl-1,2,4-triazine-3-carboxylate with norbornadiene in boiling benzene proceeded to give ethyl 5,6-diphenylpyridine-2-carboxylate in moderate yield [J. A. Elix, W. S. Wilson, R. N. Warrener, and I. C. Calder, Aust. J. Chem., 1972, **25**, 865]. In our cases, however, the use of p-xylene instead of benzene has much advantage in yields and reaction time. Namely, ethyl 5,6-diphenylpyridine-2-carboxylate was obtained in 65% yield by the reaction in boiling p-xylene for 5.5 h. On the other hand, it is confirmed by our experiment that the pyridine-2-carboxylate was formed in moderate yield (57%) after 96 h in boiling benzene.
10. H. Suda, T. Takeuchi, T. Nagatsu, M. Matsuzaki, I. Matsumoto, and H. Umezawa, Chem. Pharm. Bull., 1969, **17**, 2377.

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