

STUDIES ON as-TRIAZINE DERIVATIVES XIII¹A FACILE SYNTHESIS OF FUSARIC ACID FROM THIENYL-as-TRIAZINE
DERIVATIVE

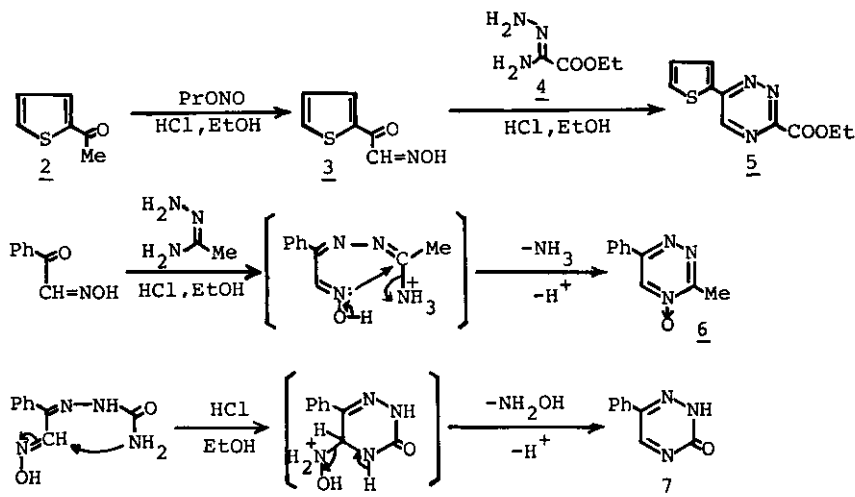
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Abstract — Reverse electron-demand Diels-Alder reaction of ethyl 6-(2-thienyl)-1,2,4-triazine-3-carboxylate with norbornadiene in boiling *p*-xylene followed by the elimination of cyclopentadiene (retro Diels-Alder reaction) gave 5-(2-thienyl)pyridine-2-carboxylate.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

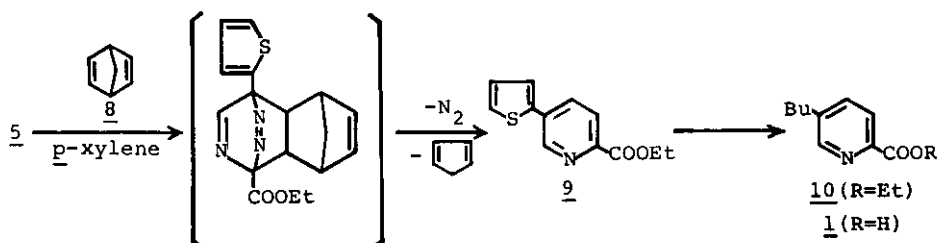
Fusaric acid (5-butylpyridine-2-carboxylic acid) (1) produced by Fusarium oxysporum is known to be a potent inhibitor for dopamine β -hydroxylase.² From the pharmaceutical point of view, the synthesis of 1 has been reported by several investigators,³ but most of these works consisted of multi-step reaction 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 reaction⁴ 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, Neunhoffer 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 [¹H-nmr(CCl₄) 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 (CHCl₃)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.

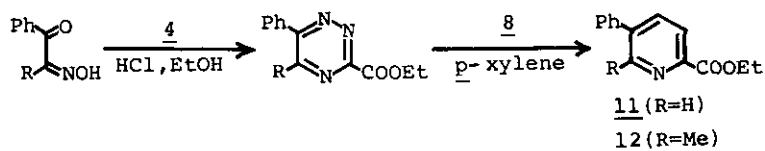


Scheme 2

The spectral data [¹H-nmr(CCl₄) 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,

$J=8\text{Hz}$), 8.43(1H,d, $J=2\text{Hz}$). 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 specimen¹⁰ 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.



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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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. Warrenner, 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.
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