Cycloaddition Reaction of Vinylfuran Derivatives

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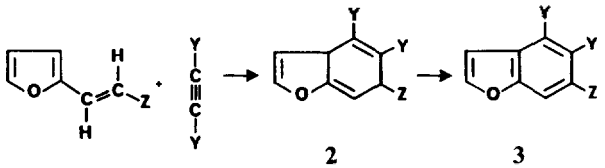
Reactions of vinyl derivatives of 5-membered heterocyclic aromatic compounds with dienophiles seem to be a suitable method for preparations of benzo derivatives of the heterocycles.[1] 2-Vinylfurans having electron-withdrawing β substituents on the vinyl group, however, did not react under various reaction conditions with maleic acid[2] or with dimethyl acetylenedicarboxylate (DMAD).[3] It has been suggested that the -I effect of the electron-withdrawing group decreases the diene character and, consequently, reaction does not take place.[2] Therefore, much vigorous reaction conditions seem to be necessary in order to force the reaction take place, if any.

Our successful preparation of dimethyl benzo[*b*]thiophene-4,6-dicarboxylate from methyl (E)-(2-thenyl)propenoate and methyl propiolate in a sealed tube at 100 ℃ for 4 days[4] led us to explore the use of a sealed tube reaction for [4+2] cycloaddition reaction with the electron-deficient dienophile system, **1a-d**. At first, we prepared *trans*-β-(2-furyl)acrylonitrile (**1a**)[5] and reexamined the cycloaddition reaction with DMAD because a nitrile group is considered as a weakly electron-withdrawing substituent. Moderate reaction conditions such as reflux in benzene for a prolonged period (4 days) did not cause any reaction between **1a** and DMAD. Even heating a neat mixture of **1a** and DMAD in a sealed-tube at 100 ℃ for 2 h did not result any change of the starting materials.



2 3

Z

1a CN
b CHO
c $COCH_3$
d $COOC_2H_5$

Y : CO_2CH_3

When a mixture of **1a** and DMAD was heated in a stainless steel tube at 185 ℃ for 5 h and the reaction mixture was chromatographed on a column of silica gel a compound (mp 136-139 ℃) was isolated in 30% in addition to the recovery of the starting materials. The structure of the product was established as **3a** with aid of NMR ($CDCl_3$) and IR (KBr) spectra. Presence of ester groups and a nitrile group was readily conformed by the peaks at 1720 and 2230 cm^{-1}, respectively, in the IR spectrum . ^{1}H-NMR spectrum showed two singlets at δ 4.03 and 4.08 corresponding to two methyl esters. In addition, a singlet of 1 H at δ 7.35 (H-7) and an apparent singlet corresponding 2 H (H-2 and H-3) are consistent with the structure **3a**. A group of peaks representing an AB pattern is expected for H-2 and H-3 of benzo[*b*] furan derivatives in general.[6] However, the chemical shifts of H-2 and H-3 are very much affected by the electronic effect of the substituent on the benzene ring. In **3a**, H-3 is on the carbon atom at the *para* position to the CN group of the benzene ring. Therefore, significant down field shift for H-3 is not surprising. The coupling constant for H-2 and H-3 is about 1-2 Hz.[6] This may be the reason that the signals corresponding to H-2 and H-3 appear as an apparent singlet at the same position. Similar pattern was observed with **3b** and **3c** in which the 6-substituents are formyl and acetyl groups, respectively. But we were not able to isolate an organic compound of similar type (**3d**) from the reaction of **1d** and DMAD.

Although the intermediates **2a-c** which should be the initial [4+2] adducts were not isolated the structures of the products (**3a-c**) seemed to be best explained by formation of **2** in the course of reaction. The present method seems to be useful because the similar type of reaction with even unsubstituted vinylfuran and DMAD was reported to give only 5% yield of [4+2] cycloaddition reaction product (Z=H in 3) under the condition of boiling in benzene for 24 h.[7]

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Refernces

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A Facile Synthesis of 2-Aminothiophene Derivatives[1]

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During the course of our research to develope a new bio-

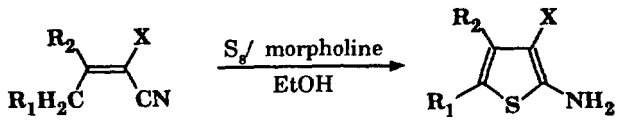

Figure 1.

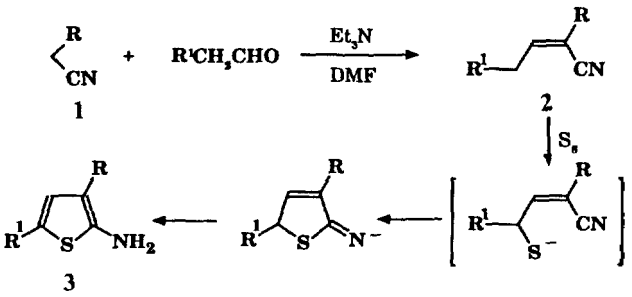

Figure 2.

logically active lead compound we needed various functionalized thiophenes. In the literature, numerous methods are available for the construction of thiophene ring systems[2]; such as oxidative cyclization of 1,3-diene-1-thiol[3], cyclization of 3-methylenethio-1-oxopropyl derivatives[4], addition of thioglycolic esters to 1,3-diketones[5], Dieckmann cyclization of 3-thiaadipic acid derivatives[6] and ring closure of unsaturated nitriles with sulfur (Gewald Synthesis).[7]

Most of the exisisting methods except those of Gewald, however, possess severe limitation due to either harsh reaction condition or difficulties to obtain staring material. So, further research to develope better synthetic methodologies are certainly warranted. In this context Gewald's method deserves some mention. He treated α,β-unsaturated nitriles, which are available by condensation of activated cyanomethylene derivatives, with elemental sulfur in ethanol containing a base to produce the corresponding 3-substituted 2-amino thiophenes (Figure 1).

After careful thought, however, it was envisioned that the aforementioned compounds may be obtained simply by condensing active methylene compounds, *e.g.*, α-cyano ethylacetate, with aldehyde in the presence of sulfur without isolating the α,β-unsaturated nitriles as an intermediate in a single one-pot process. Indeed it turned out to be successful efforts and its synthetic scheme, and the results are shown in Figure 2 and Table 1, respectively. However, it should be noted that the attempts to prepare 2-*hydroxy* thiophenes starting from either diethyl malonate or diethyl carboethoxymethyl phosphonate were not fruitful. Although the compounds 3 were known in prior art as mentioned above,[8] each compound was fully identified by ^{1}H NMR and mass spectroscopy.

The preparation of entry 1 is a typified procedure. To a solution of ethyl cyanoacetate (5 g, 44.2 mmol), n-butylaldehyde (3.9 m*l*, 44.2 mmol) were added triethylamine (6.2 m*l*, 44.2 mmol) and DMF (6.8 m*l*, 88.4 mmol). After stirring 30 min sulfur powder (1.4 g, 44.2 mmol) was added. The resulting suspension was stirred at r.t. overnight. Water (100 m*l*) was added and the reaction mixture was extracted with ether (50 m*l* × 3). The combined ether extracts were washed with brine (100 m*l* × 1), dried over $MgSO_4$ and passed through short path of silica gel. Concentration of the filtrates *in vacuo* gives practically pure product (6.5 g, 73% yield) as yellow solid. mp. 59-62℃; ^{1}H-NMR (80 MHz) δ 1.25(t, 3H), 1.30(t, 3H), 2.57(q, 2H), 4.25(q, 2H), 5.20(−NH_2), 6.60(s, 1H); M/S 200.

Table 1. Preparation of 2-Aminothiophenes (3) from Cyano Derivatives (1) and Varione Aldehydes

Entry	R	R^1	Yield[a] (%)
1	CO_2Et	Et	73
2	CO_2Et	*i*Pr	92
3	CO_2Et	Ph	43
4	$P(O)(OEt)_2$	Et	51
5	$P(O)(OEt)_2$	Me	52
6	$P(O)(OEt)_2$	Ph	37

[a] Not optimized, but purified and isolated yield.

With these 2-amino-5-substituted thiazoles in hand we are now actively involved in designing biologically active compounds containing thiophene moiety. The resulting progress will be reported in due course.

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Absolute Configuration of Panaxydol

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Panax ginseng C. A. Meyer (Araliaceae) has been known