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CERTAIN CINNAMONITRILES REACT WITH 2-METHOXYFURAN TO PRODUCE A NEW PHENYLCYCLOPROPANE PRODUCT

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Abstract- 2-Methoxyfuran as a diene fails to generate a Diels-Alder adduct when it reacts with β-cyanostyrenes (cinnamonitriles). However, in the reaction with β-cyanostyrenes possessing additional electron-withdrawing groups (CN, CO_2Et, SO_2Ph and COPh), it yielded two new phenylcyclopropanes. The formation of the cyclopropane ring may occur through the opening of the furan ring in the β-cyanostyrene-furan complex (zwitterion) formed. The product formation process involves a sterically controlled intramolecular reaction.

INTRODUCTION

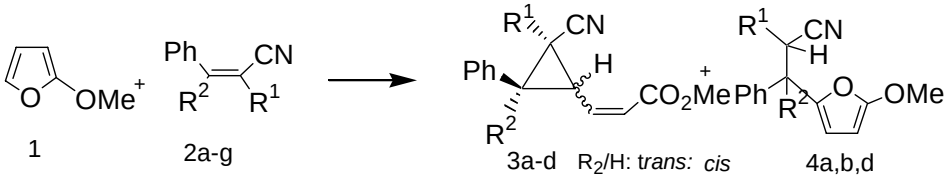
Styrenes are known as dienophile reagents in the Diels-Alder reaction[1] used for the construction of a *C*-glycopyranoside,[2] but use of high pressure[3] or Lewis acid catalysis[4] have been the drawback inherent in the reaction in their use. To this end, we have been studying the Diels-Alder reactions of furans with some electron-deficient dienophiles.[5] Recently, we reported that 2-methoxyfuran reacts with β-nitrostyrenes to give not only the Michael adducts, but also the unexpected new isoxazoline *N*-oxide,[6] without the formation of a Diels-Alder adduct. During this work, we explored the use of β-cyanostyrenes as a powerful dienophile for this reaction.[7] In the present report, we describe some interesting new reaction of β-cyanostyrenes that differ from those previously seen with β-nitrostyrenes.[6]

We initially found that the cyanostyrenes did not react with furan or 2-methylfuran; therefore, in the present study, we chose 2-methoxyfuran as a more reactive diene (Scheme 1). The following is a typical experimental procedure. To a stirred solution of 2-methoxyfuran (**1**, 2.5 mmol) in chloroform (3 mL) was added ethyl 1-cyanocinnamate (**2a**, 1.2 mmol) at room temperature under a nitrogen atmosphere. After being stirred for 4 days, the resulting mixture was concentrated under reduced pressure to give an oil,

which was separated by column chromatography on silica gel (eluent solvent: ethyl acetate / hexane, 1/ 4).

The results of the reactions of 2-methoxyfuran (**1**) with various β-cyanostyrenes (**2**) are given in Table 1. In general, the β-cyanostyrenes with a relatively weak electron-withdrawing group (**2e**, **2f, 2g**) failed to produce an adduct with 2-methoxyfuran, even after a reaction time of one week (Table 1, Runs 5 ~ 7). However, we expected that β-cyanostyrene derivatives with a stronger electron-withdrawing group (**2a** ~ **2d**) might react with **1** to give the adducts, as was the case in previous reaction with electron deficient dienophiles.

Ethyl 1-cyanocinnamate (**2a**) produced a mixture of the adducts (*trans*-**3a**, *cis*-**3a** 46% yield, and **4a** 5% yield, Run 1 in Table 1). In contrast to the results with β-nitrostyrene,[6] the reaction of **1** with **2a** gave neither Diels-Alder adducts, nor a heterocyclopentane derivative. The adducts (**3a**) showed no evidence of a furan ring and imino group signals in their NMR spectra. The ^{1}H- and ^{13}C-NMR spectra of the main adduct indicate the presence of the methyl ester group (CO_2CH_3: δ =3.73 ppm, s, 3H, and 63.3, 165.1 ppm) and the vinyl group (CH=CH, *cis* configuration: δ =6.00 ppm, dd, *J*=1.0, 11.7Hz and δ =6.24 ppm, dd, *J*=9.3, 11.7Hz).[8] Further, the *cis* configuration was confirmed by NOE experiment. These signals



For **2**, **3**, **4**: a, R^1=CO_2Et , R^2=H; b, R^1=CN, R^2=H; c, R^1=COPh, R^2=H; d, R^1=SO_2Ph, R^2=H; e, R^1=CN, R^2=Me; f, R^1=CO_2H, R^2=H; g, R^1=$CONH_2$, R^2=H; h, CN→ COMe, R^1=COMe, R^2=H

Scheme 1 The reaction of β-cyanostyrene (**2**) and related compounds with 2-methoxyfuran (**1**)

Table 1 Reaction of β-cyanostyrenes and related compounds (**2**) with 2-methoxyfuran (**1**)

Run	cyanostyrene	cyclopropane (yield, %)	*trans*/*cis*	Michael adduct (yield, %)
1	**2a**	**3a** (46)	3.5 / 1.0	**4a** (5)
2	**2b**	**3b** (84)	4.5 / 1.0	**4b** (8)
3	**2c**	**3c** (50)	1.5 / 1.0	trace
4	**2d**	**3d** (77)	1.0/ 1.3	**4d** (5)
5	**2e**	no reaction		
6	**2f**	no reaction		
7	**2g**	no reaction		
8	**2h** [a)]	(36)	3.3/1.0	(51)

[a)]: β, β'-diacetylstyrene. All compounds gave satisfactory spectroscopic data.

indicate that scission of the furan ring had occurred. Furthermore, the proton signal at higher field (δ=4.44 ppm, ddd, 1H, *J*=1.0, 8.3, 9.3 Hz) is correlated with an H-atom of the vinyl group (δ=6.24 ppm, dd, *J*=9.3, 11.7 Hz). Finally, the structure of the main adduct was determined by single crystal X-Ray diffraction to be a vinylcyclopropane derivative (Figure 1).[9] The main adduct shows a *trans* (*anti*) configuration between the hydrogen atoms of the cyclopropane ring. On the other hand, the stereochemistry of the minor adduct was found to have a *cis* (*syn*) configuration (prominent NOE signals from protons with δ =3.48ppm, d, *J*=9.7 Hz, and δ =4.17 ppm, dd, *J*=9.7, 10.3 Hz.).

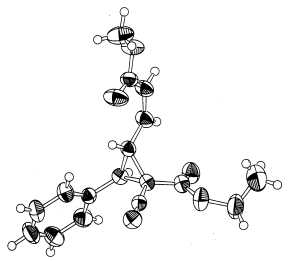


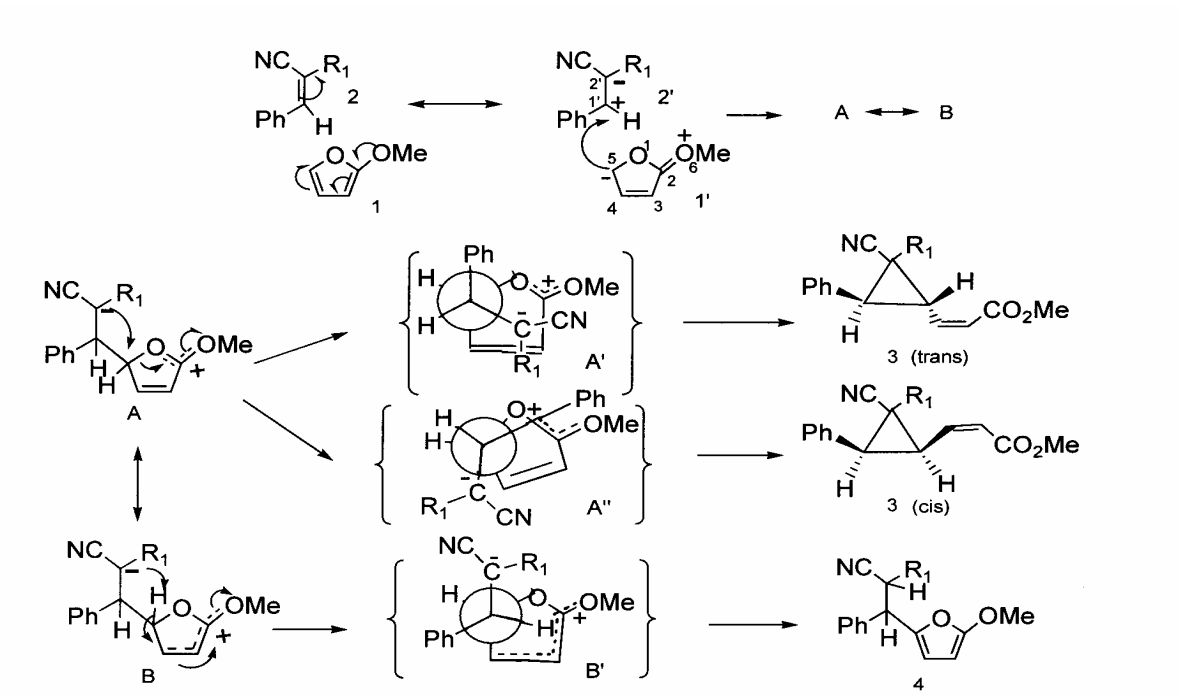
Figure 1

Similar stereoselectivity was also observed in the reaction of **1** with the other electron-deficient cyanostyrenes (**2b** ~ **d**). However, in the case of the compounds (**2c**, **d**) bearing bulky benzoyl and phenylsulfonyl groups, the amounts of the *trans* and the *cis* cyclopropanes[10] are almost equal. These informative results imply that the product formation process involves a sterically controlled inter- or intramolecular reaction.

The processes shown in Scheme 2 may plausibly account for the formation of the cyclopropane ring and the Michael adduct.[11] The mesomeric form (**1'**) of 2-methoxy- furan (**1**) attacks the 1'-position of the styrene (**2**) to give the polarized β-cyanostyrene-furan adduct (two mesomeric isomers of the zwitterions (**A** and **B**)).[12] In the zwitterion (**A**)**,** in which the cation is delocalized at the O1-C2-O6 of the furan, an intramolecular nucleophilic substitution (S_N2 type) may be responsible for the opening of the furan ring (O1-C5 bond cleavage) and simultaneous forming of the cyclopropane ring. The *trans*-cyclopropane is produced from **A** taking the conformer (**A'**) in Scheme 2, which has a *gauche* conformation between the H1' of the styrene and H5 of the furan. On the other hand, the *cis*–product is produced from the other conformer (**A"**), which has a *synclinal* conformation between the H1' and H5. Therefore, the intramolecular nucleophilic substitution proceeds by a S_N2 mechanism which, under stereocontrol, preferentially produces a *trans* configuration at the position between the hydrogens because of the steric repulsion between the phenyl group and the forming vinyl ester group (Figure 2). However, in the case of the cyanostyrenes bearing bulky groups (COPh, SO_2Ph), the cyano carbanion attack on the allyl carbon must occur in a direction which avoids the steric repulsion between the bulky group and the vinyl ester group. The occurrence of an attack in that direction would favor the *cis* configuration. Calculations of strain energy predict such an effect.[13] Therefore, the two competing effects may lead to equal amounts of the *trans* and *cis* products.

In the other zwitterion (**B**), in which the cation is delocalized over the C4-C3-C2-C6 atoms of the furan, nucleophilic substitution may have occurred to cause a shift of the H at 5-position to give the Michael adduct. The adduct is produced from **B** taking the conformer (**B'**) in Scheme 2, which has an *anti* conformation between the H1' and the H5. The structure of the conformer (**B'**) shows that the distance between the C2' carbon and the H5 hydrogen is about 2.5 Å,[13] providing a conformation that allows the

reaction to proceed smoothly giving the Michael adduct.



Scheme 2 The process for the formation of the cyclopropane (**3**) and the Michael adduct (**4**)

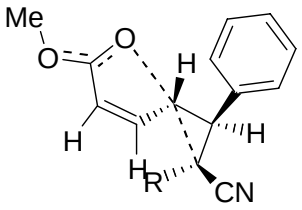


Figure 2 The transition state structure (A', R=CN)

Huisgen *et al.* [11] have reported that the use of ethylene substituted with only very strongly electrophilic groups (two trifluoromethylene and two cyano groups) leads to the formation of a cyclopropane ring with 2-methoxyfuran. The high yield of the isolated product, coupled with the disappearance in a few seconds at low temperatures of the strong color associated with charge-transfer, indicate that these strongly electrophilic groups may stabilize the initially formed intermediate. Moreover, our reaction is able to exploit variations in the stability of the initially formed ethylene intermediate resulting from the steric and the electronic effect of the phenyl group.

Therefore, we are currently conducting further investigations of rearrangements utilizing styrenes with non-cyano groups (e.g. Run 8 in Table 1, **2h**:β,β'-diacetylstyrene) and the reaction of Run 8 indicates their possible applications in the cases where styrenes have powerful electron-withdrawing groups.

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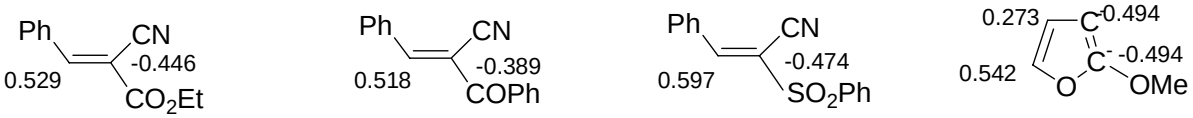
8. The spectral data of the adduct. **Main** product (*trans*-**3a**): mp: 65.5 ~ 66.5 ºC (Ethyl acetate/ Hexane). MS: m/z, 299(M^+), 267(M^+-MeOH), 253, 221(M^+-Ph), 195, 194, 167, 166, 139, 128, 115, 98. IR: 3028, 2946, 1734, 1702, 1618, 1584, 1360, 1260, 1198 cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$): δ =1.28 (3H, t, *J*=7.3 Hz), 3.36 (1H, d, *J*=8.3 Hz), 3.73 (3H, s), 4.24 (2H, q, *J*=7.3 Hz), 4.44 (1H, ddd, J=1.0, 8.3, 9.3 Hz), 6.00 (1H, dd, *J*=1.0, 11.7 Hz), 6.24 (1H, dd, *J*=9.3, 11.7 Hz), 7.24 ~ 7.45 (5H, m) ppm. ^{13}C-NMR (62.5 MHz, $CDCl_3$): δ=14.1, 30.2, 34.4, 40.1, 51.7, 63.3, 115.6, 124.2, 128.4, 128.7, 128.9, 130.1, 132.2, 140.0, 165.1, 166.2 ppm. Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.22; H,: 5.72; N, 4.68. Found: C, 68.06; H, 5.63; N, 4.44. **Minor product** (*cis*-**3a**): ^{1}H-NMR (250 MHz, $CDCl_3$): δ=1.32 (3H, t, *J*=7.3 Hz), 3.48 (1H, d, *J*=9.7 Hz), 3.72 (3H, s), 4.17 (1H, dd, *J*=9.7, 10.3 Hz), 4.28 (2H, q, *J*=7.3 Hz), 5.76 (1H, dd, *J*=10.3, 11.7 Hz), 6.04 (1H, dd, *J*=1.0, 11.7 Hz), 7.24 ~ 7.45 (5H, m) ppm. ^{13}C-NMR (62.5 MHz, $CDCl_3$): δ=14.1, 28.1, 33.2, 38.4, 51.7, 63.4, 114.9, 124.4, 128.4, 128.7, 128.9, 129.3, 130.5, 139.9, 166.2, 166.5 ppm. **Michael adduct** (**4a**): ^{1}H-NMR (250 MHz, $CDCl_3$): δ=1.30(3H, t, *J*=7.3 Hz), 3.82 (3H, s), 4.25(2H, q, *J*=7.3 Hz), 4.38 (1H, d, *J*=7.6 Hz), 4.49 (1H, dd, *J*=0.4, 7.6 Hz), 5.12 (1H, d *J*=3.3 Hz), 6.21(1H, dd, *J*=0.4, 3.3 Hz), 7.39 ~ 7.45 (5H, m) ppm. ^{13}C-NMR (62.5 MHz, $CDCl_3$): δ=13.8, 46.4, 55.8, 57.9, 80.5, 111.4, 128.3, 128.5, 129.3, 129.5, 134.5, 134.7, 138.9, 162.1, 164.8 ppm.
   3b: Anal. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found: C: 71.38, H: 4.79, N: 11.00.
   3c: Anal. Calcd for $C_{20}H_{17}NO_3$: C, 75.22; H, 5.37; N, 4.39. Found: C, 75.42; H, 5.30; N, 4.25.
   3d: Anal. Calcd for $C_{20}H_{17}NO_4S$: C, 65.38; H, 4.66; N, 3.81. Found: C, 65.51; H, 4 .51; N, 3.67.
   3h: Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.36; H, 6.16.
9. X-Ray crystallographic analysis was carried out on a Rigaku AFC5R diffractometer. The diffraction data were collected with MoKα radiation and 3343 independent reflections were used to solve the structure by the teXsan program.[15] All non-H atoms were located by direct methods using SIR92[16] and refined anisotropically. Crystal data for $C_{17}H_{17}NO_4$: formular weight, 319.31, triclinic space group P-1, a=9.753(7)Å, b= 10.28(1)Å, c=9.25(1)Å, α=106.0(2)º, β=106.0(2)º, γ=94.13(8)º, U=828(1)$Å^3$, Z=2, Dcalc=1.28 gcm^{-3}, R= 0.128 (Rw=01082.) for 3533 refection data point with I>1σ and 1996 variables. CCDC No.291612.
10. The structure of 2-cyano-3-phenylcyclopropane (**3d**) was determined by the X-Ray crystallo-

graphic analysis. K. Itoh and S. Iwata, *Z. Kristallogr. N.C.S.*, 2004, **219**, 455. CCDC No. 1267/1382.

11. R. Huigen *et al.* indicated the formation of a cyclopropane *via* the zwitterionic intermediate at the reactions of the furans and the ethylene derivatives. We calculated the potential energy for the transition state of Figure 2 using the PM3 method. It is the appropriate value: 36.9 kcal/mol.
G. U-Desmaison, G. Mloston, and R. Huigen, *Tetrahedron Lett.*, 1994, **35**, 4977; G. Mloston and R. Huisgen, *J. Heterocycl. Chem.*, 1994, **31**, 1279.
12. The regioselectivity for the reaction can be predicted from the calculated orbital coefficient of the olefinic carbon atoms and the furan atoms. Furthermore, the secondary orbital interactions found by a PM3 calculation using Spartan v. 4.0.1, led us to expect a stereoselective outcome.



The calculated orbital coefficients of the olefinic carbon atoms

13. In general, the MM3 strain energy of the *trans* product is smaller than that of the *cis* isomer. However, in the case of β-phenylsulfonylcyanostyrene, the energy of the *trans* product is larger than that of the *cis* isomer. (△1.09 kcal/mol) The MM3 strain energy was calculated using CAChe ver. 4.4 (Oxford Molecular Limited).
14. The distance is calculated by a PM3 method using Spartan v. 4.0.1.
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