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DONOR-SUBSTITUTED FURANS AND 1,2-BIS(TRIFLUOROMETHYL)ETHYLENE-1,2-DICARBONITRILE: A NOVEL REARRANGEMENT AND ITS STERIC COURSE

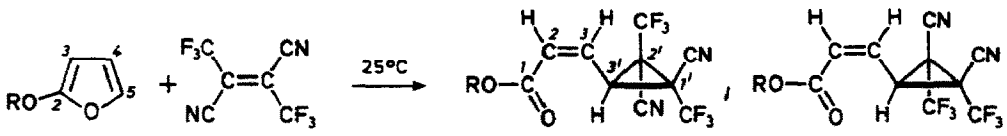
Gonzalo Urrutia-Desmaison,[1] Grzegorz Mloston,[2] and Rolf Huisgen *

Institut für Organische Chemie der Universität München
Karlstr. 23, D-80333 München, Germany

Abstract Opening of the furan ring and concomitant closure of a cyclopropane ring was observed in the reaction of 2-methoxy- and 2-*p*-tolyloxyfuran with 2,3-bis(trifluoromethyl)fumaronitrile (*trans*-BTE). Electrophilic 5-attack gives rise to a zwitterion which can rotate about the acceptor bond, dissociate to reactants, or furnish diastereoisomeric *cis*-3-cyclopropylacrylates. In the presence of pyridine, 1,3-prototropy converts the zwitterion to 5-substituted furans.

Normal Diels-Alder reactions are fast if the diene is electron-rich and the dienophile electron-deficient; the interaction is controlled by HO(diene) - LU(dienophile) [3]. However, in extreme cases the "two-bond nucleophilicity" of the diene may be superseded by the "one-bond nucleophilicity".[4]

In the reaction of 2-methoxyfuran (**1**, 1.1 equiv) with pure 2,3-bis(trifluoromethyl)fumaronitrile [5] (*trans*-BTE, **3**, sublimed and twice recryst. from CS_2) in $CDCl_3$ at 25°C, the orangered charge-transfer color faded in several hours. Quantitative ^{19}F NMR analysis with trifluoroanisole as weight standard revealed complete formation of the *cis*-3-substituted methyl acrylates **4** and **6** (77:23) containing *trans*- or *cis*-located CF_3 groups at the newly formed cyclopropane ring. After distillation at 90°C/0.2 torr the diastereoisomers were separated by thick-layer chromatography (tlc) on silica gel; **4** was crystalline (mp 44-46°C), and **6** remained oily.[6]



1 R = CH_3 **3** (*trans*-BTE) **4** R = CH_3 **6**
2 R = *p*-$CH_3C_6H_4$ **5** R = *p*-$CH_3C_6H_4$ **7**

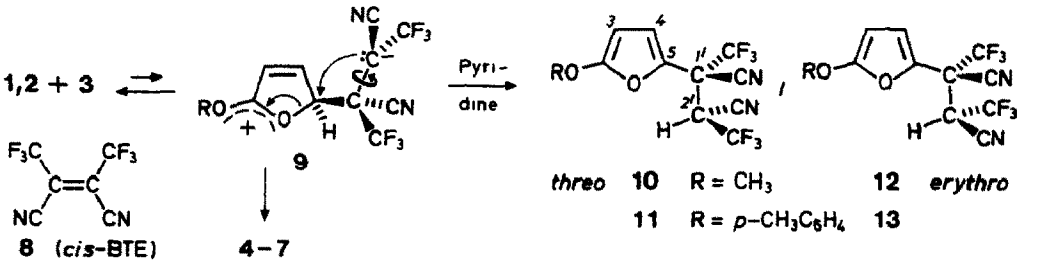
A slower opening of the furan ring was observed with 2-*p*-tolyloxyfuran (**2**, 1.3 equiv) [7] and pure *trans*-BTE ($CDCl_3$, r.t.). The ^{19}F NMR spectrum after 14 d indicated 86% of the *p*-tolyl acrylates **5** and **7** in the ratio of 76:24; 3% of the substituted furans **11** and **13** occurred, and 6% of **3** being still unconsumed. An analogous work-up afforded pure **5** (mp 42-43°C) and **7** (mp 90-92°C).

IR frequencies of 1722 and 1726 cm^{-1} for **4** and **6** reveal a conjugated ester carbonyl. The 2-H and 3-H signals appear at δ_H 6.42 and 6.15 with $J_{2,3}$ = 11.1 Hz for **4**, and 6.51, 6.12, $J_{2,3}$ = 10.9 Hz, for

6. These are *cis*-vinylic couplings; J_{cis} for methyl acrylate amounts to 10.2 Hz whereas $J_{3,4}$ = 3.5 Hz for 2-methoxyfuran is much smaller. The multiplicity of the 3-H signal is dd ($J_{3,3'}$ = 7.2 Hz) for **6**, but ddq ($J_{3,3'}$ = 6.7 Hz, $^5J_{H,F}$ = 2.3 Hz) for **4**. Fluorine couplings are transmitted through space, and a *cis-vic* relation of 2'-CF_3 and the acrylic ester residue at C-3' in **4** is diagnosed from the long range H,F coupling.

The cyclopropane **4** is chiral, and **6** contains a plane of symmetry. The stereochemistry is reflected by δ_C 29.6, 31.2 (C-1', C-2', $^2J_{C,F}$ = 39 Hz) and 31.4 (C-3', $^3J_{C,F}$ = 1.9 Hz) for **4** as well as by 34.3 (C-1' + C-2', $^2J_{C,F}$ = 45 Hz) and 29.3 (C-3', $^3J_{C,F} \sim 2$ Hz) for **6**; the low δ_C values are indicative of the three-membered ring. Only the diastereoisomer **4** with *trans*-located CF_3 groups shows *non-equivalent* pairs of CF_3 and CN groups.

The ^{19}F NMR spectrum of **4** consists of a d at δ -61.3 (2'-CF_3) and s at -65.8 (1'-CF_3); the lack of F,F coupling is consistent with *trans*-CF_3 groups at the cyclopropane ring. The equivalence of 1'-CF_3 and 2'-CF_3 in **6** gives rise to s at δ_F -61.9. There is no coupling between the CF_3-groups and the vinylic 3-H in **6**, thus excluding a third conceivable stereoisomer with *all-cis* relation of substituents at the three-membered ring. The NMR data of the *p*-tolyl acrylates **5** and **7** are closely related.

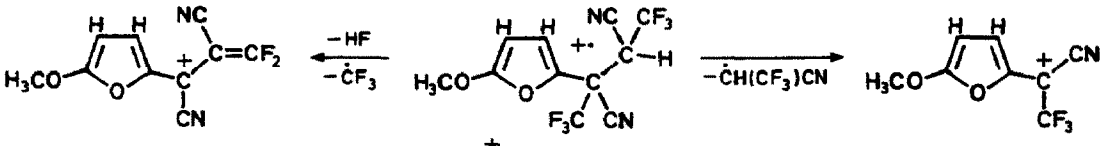


Zwitterion **9** resulting from the electrophilic attack of **3** at the furan-5-position is a plausible intermediate. An intramolecular nucleophilic substitution (S_N2 type) may be responsible for the opening of the furan ring and the simultaneous closing of the three-membered ring. When *cis*-BTE **8** was reacted with the nucleophilic furans **1** and **2**, its equilibration with *trans*-BTE (**3**/**8** = 95:5) was much faster than the opening of the heterocycle which furnished virtually the same ratios of **4**/**6** and **5**/**7**, respectively, as observed with *trans*-BTE **3** [8]. Thus, the *reversible* dissociation and the *irreversible* intramolecular substitution are taking place from an established rotational equilibrium of **9** about the marked bond.

Concentration measurements by ^{19}F NMR analysis in $CDCl_3$ at 25°C afforded the rate constants for the opening of the furan ring with *trans*-BTE: k_2 = 6.6 10^{-4} $M^{-1}s^{-1}$ for **1** and 7.6 10^{-6} $M^{-1}s^{-1}$ for **2**. Thus, the heterocycle of the more nucleophilic **1** is opened 85 times faster than that of **2**. These overall k_2 values pertain to the reversible electrophilic attack *and* the substitutive ring-opening (see formula scheme). The influence of solvent polarity is positive: cyclopropane formation from **2** + **3** in nitromethane was 30 times faster than in $CDCl_3$.

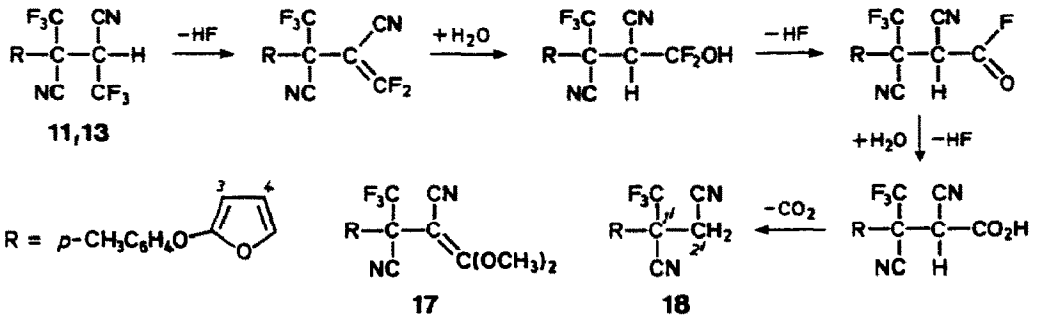
The zwitterion **9** can regain furan aromaticity by base-catalyzed 1,3-prototropy. When the reaction of **1** or **2** with *trans*-BTE was run in the presence of 0.24 equiv of pyridine, cyclopropane formation

was suppressed in favor of the substitution products **10** + **12** and **11** + **13**, respectively. Only **12** was obtained crystalline (mp 73-75°C); the lability towards silicagel (see below) thwarted the chromatographic separation. The ^{1}H NMR spectra signaled furan derivatives, e.g., two d at δ_H 5.32 (3-H) and 6.85 (4-H) with $J_{3,4}$ = 3.5 Hz for **11**; the q at δ_H 4.38 (2'-H) displays the coupling by CF_3 ($J_{H,F}$ = 6.1 Hz). The tentative assignment of *threo* and *erythro* configurations (60:40) is based on the premise that conformations with an intramolecular hydrogen bond of the acidic 2'-H with the furan oxygen play a major role.[9] In the system **2** + *trans*-BTE in $CDCl_3$ at 25°C, 0.50 M in pyridine, the rate of BTE consumption was measured: k_2 = 1.0 10^{-3} $M^{-1}s^{-1}$ is 130 times higher than k_2 for the opening of the furan ring.



14 **15** **16**

The MS (70 eV, 25°C) of **10,12** reveals two major pathways from the molecular radical ion **15** to stabilized onium ions. The elimination of HF, followed by loss of CF_3, provides **14** with its oxonium, allylic and benzylic resonance as the parent peak. The breaking of the central C–C bond of the pentasubstituted ethane furnishing **16** has a share of 97%. A fragment $C_4H_2O_2$ (*m/z* 82, 18%) is probably $\overset{+}{O}{\equiv}C-CH=CH-\dot{C}=O$. All the formulae were secured by high resolution.

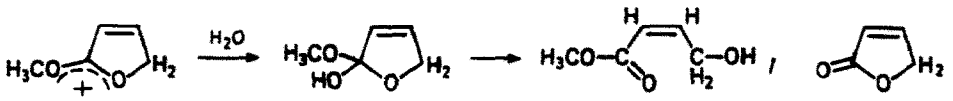


11,13 **17** **18**

Surprisingly, the attempt of separating the *threo* and *erythro* forms, **11** and **13**, by tlc on silicagel led (after distillation at 110°C/0.001 torr) to 72% of **18** in which the 2'-CF_3 is formally replaced by H. The CH_2 group appears as an AB spectrum at δ_H 3.29 and 3.38 with J_{gem} = 16.8 Hz. The C-2' of *threo*-**11** at δ_C 41.8 ($^2J_{C,F}$ = 33.9 Hz) is shifted in **18** to 22.5 ($^3J_{C,F}$ ~ 2 Hz) whereas the C-1' signal has hardly changed (δ_C 48.4 with $^2J_{C,F}$ = 32.4 Hz in **11** and 46.6 with $^2J_{C,F}$ = 32.3 Hz in **18**). Two d at δ_H 5.55 and 6.80 (J = 3.5 Hz) for 3-H and 4-H establish the intact furan ring of **18**.

A plausible solution of the "whodunit" is depicted in the formula scheme above. In contrast to general belief, commercial silicagels are basic [10] and can deprotonate **11/13** and intermediate species. The conversion of **11/13** to **17** (38%) with 2 equiv of sodium methoxide in methanol may follow a simi-

lar mechanistic pattern. The ketene acetal **17** shows the OCH_3 signals at δ_H 3.87 and 4.25; the remaining CF_3 occurs as d at δ_F -70.8, coupled by the 4-H of the furan with 0.9 Hz.



19 **20** **21** **22**

Dilute HCl in aqueous DMSO catalyzes the hydrolysis of **1**; 16% of methyl 4-hydroxy-*cis*-crotonate (**21**) and 60% crotonolactone (**22**) were reported;[11] the mechanism via **19** and **20** is not closely related to our ring opening. Greater is the similarity with the ring opening of 5-alkoxyoxazoles with TCNE, triazolinedione or other electrophilic double bonds;[12] however, in the stabilization of the intermediate zwitterions, no three-membered rings are formed. The closure of the cyclopropane ring by substitution, **9** → **4** - **7**, reminds of the first synthesis of a cyclopropane from the anion of diethyl 2-bromoethylmalonate carried out by W. H. Perkin jr. in the Munich laboratory 110 years ago.[13]

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8. *cis*-BTE, obtained by preparative GC of the *trans,cis* mixture, contains an impurity that catalyzes the 1,3-prototropy of **9**. *cis*-BTE (**8**) + 1.6 equiv of **1** in $CDCl_3$ at 25°C gave after 2 h 61% **4** + **6** (79:21) besides 18% **10** + **12** (60:40).
9. The acidity of the 2'-H in the mixture **11** + **13** was demonstrated by slow H,D exchange (72% in 24 h) with D_2O in $CDCl_3$. In the H chelate of the *threo* form **11**, the CF_3 groups occupy quasi-*anti* positions and do not show F,F coupling; s at δ_F -68.93 and d at -64.58, split by 2'-H with 5.9 Hz. In contrast, the *erythro* form **13** shows q at δ_F -68.88 (J_{FF} = 6.1 Hz) and a quintet at -63.78 due to $J_{FF} = J_{FH}$ = 6.2 Hz. Thus, the smaller distance of the *gauche* CF_3 groups in **13** allows F,F-coupling. The ^{19}F NMR data for the pair **10**/**12** are very similar.
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