JOC*Note*

Unexpected Formation of Tetrasubstituted 2,3-Dihydrofurans from the Reactions of β-Keto Polyfluoroalkanesulfones with Aldehydes

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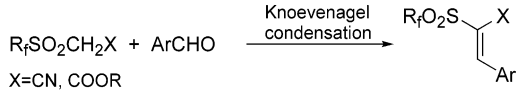
Received April 23, 2004

Abstract: Catalyzed by piperidine, the reactions of β-keto polyfluoroalkanesulfones with aromatic aldehydes afforded the unexpected tetrasubstituted 2,3-dihydrofurans in good yields, probably proceeding through the normal Knoevenagel condensation products. This reaction provided an efficient and novel method for the stereoselective synthesis of fluorine-containing tetrasubstituted *trans*-2,3-dihydrofurans.

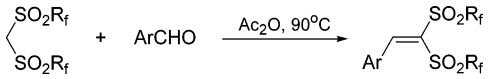
Per(poly)fluoroalkanesulfonyl groups, R_fSO_2, are one of the strongest electron-withdrawing groups which can activate α-C−H bonds and adjacent olefins or function as nucleofugic leaving groups having an electron pair to form sulfinate anions.[1] Due to their manifold reactivities, per(poly)fluoroalkanesulfonyl groups are of special interest in organic chemistry, especially in organofluorine chemistry. α-Perfluoroalkanesulfonyl acetate esters are moderately active methylene compounds that are widely used in the synthesis of heterocycles and unsaturated sulfonyl esters.[2] The Knoevenagel condensation reaction between α-perfluoroalkanesulfonyl acetate esters or β-keto aryl sulfones and aldehydes is well-known. Recently, Hanack[2] and others[3] reported that perfluoroalkanesulfonyl acetonitriles and esters can easily undergo Knoevenagel condensation with aromatic aldehydes to give 2-aryl-1-perfluoroalkanesulfonyl acrylonitriles and 3-aryl-2-perfluoroalkanesulfonyl-2-propenoates (Scheme 1).

In 1973, Koshar et al. reported improved and convenient methods for preparing bis(perfluoroalkylsulfonyl)-methanes from perfluoroalkylsulfonyl fluorides and preparing a variety of substituted β-disulfones by organometallic reactions, alkylations, and halogenations of the methylene disulfones or derivatives.[4] Our laboratory has also studied chemical transformations of these compounds.[5] We found that the reactions of bis(perfluoroalkanesulfonyl)methanes with aromatic aldehydes provided Knoevenagel condensation products (Scheme 2).[5d]

SCHEME 1



SCHEME 2



In this paper, we report the unexpected formation of tetrasubstituted *trans*-2,3-dihydrofurans under Biginelli[7] or Knoevenagel condensation reaction conditions when β-keto polyfluoroalkanesulfones such as $R_fSO_2CH_2COR$ ($R_f = ClC_4F_8$, R = Ph (**1a**) or CH_3 (**1b**)) are reacted with aromatic aldehydes. Our results are somewhat related to those of Calo et al.,[6] who reported that reactions of β-keto sulfides with aldehydes in ionic liquids also directly afford tetrasubstituted 2,3-dihydrofurans. The importance of dihydrofuran derivatives is apparent as they are present in a large variety of naturally occurring substances and are precursors of furans by oxidation.[8] In addition, the introduction of fluoroalkanesufonyl group on dihydrofuran may confer improved biological or physical activities.

Initially, we tried to synthesize polyfluoroalkanesulfonyl-substituted dihydropyrimidinones by the Biginelli reaction.[7] When a mixture of **1a**, benzaldehyde (**2a**), and urea was refluxed for 24 h in ethanol, one solid product was isolated by chromatography column in low yield. To our surprise, the ^{1}H NMR showed it had 17 protons, which is more than we expected. Moreover, D_2O-exchanging experiments did not show activated protons in this compound. It was clear that the product is not the expected dihydropyrimidinone derivative, which has only 13 protons, two of which could be exchanged by D_2O. On the basis of the NMR spectral data and elemental analysis, the product was identified as the dihydrofuran derivative 2-benzoyl-4-(4-chloro-1,1,2,2,3,3,4,4-octafluorobutane-1-sulfonyl)-3,5-diphenyl-2,3-dihydrofuran **3aa**. Encouraged by the unexpected formation of a dihydrofuran derivative, we tried to optimize this reaction.

(1) (a) Hendrickson, J. B.; Bergeron, R.; Giga, A.; Sternbach, D. *J. Am. Chem. Soc.* **1973**, *95*, 3412. (b) Hendrickson, J. B.; Giga, A.; Wareing, J. *J. Am. Chem. Soc.* **1974**, *96*, 2275. (c) Bordwell, F. G.; Vanier, N. R.; Matthews, W. S.; Hendrickson, J. B.; Skipper, P. L. *J. Am. Chem. Soc.* **1975**, *97*, 7160. (d) Hendrickson, J. B.; Boudreaux, G. J.; Palumbo, P. S. *J. Am. Chem. Soc.* **1986**, *108*, 2358. (e) Hendrickson, J. B.; Sternbarch, D. D.; Bair, K. W. *Acc. Chem. Res.* **1977**, *10*, 306.

(2) (a) Hanack, M.; Bailer, G.; Hackenberg, J.; Subramanian, L. R. *Synthesis* **1991**, 1205. (b) Menke, O.; Steinhuber, E.; Martinez, A. G.; Subramanian, L. R.; Hanack, M. *Synthesis* **1994**, 1291.

(3) Goumont, R.; Magder, K.; Tordeux, M.; Marrot, J.; Terrier, F.; Wakselman, C. *Eur. J. Org. Chem.* **1999**, 2969.

(4) Koshar, R. J.; Mitsch, R. A. *J. Org. Chem.* **1973**, *38*, 3358.

(5) (a) Zhu, S. Z.; Xu, G. L.; Qin, C. Y.; Xu, Y.; Chu, Q. L.; DesMarteau, D. D. *Heteroatom Chem.* **1999**, *10*, 147. (b) Zhu, S. Z.; Pennington, W. T.; DesMarteau, D. D. *Inorg. Chem.* **1995**, *34*, 792. (c) Zhu, S. Z. *Heteroatom Chemistry* **1994**, *5*, 9. (d) Zhu, S. Z. *Synthesis* **1994**, 261. (e) Zhu, S. Z. *J. Fluorine Chem.* **1993**, *64*, 47. (f) Zhu, S. Z.; Li, A. W. *J. Fluorine Chem.* **1993**, *60*, 175.

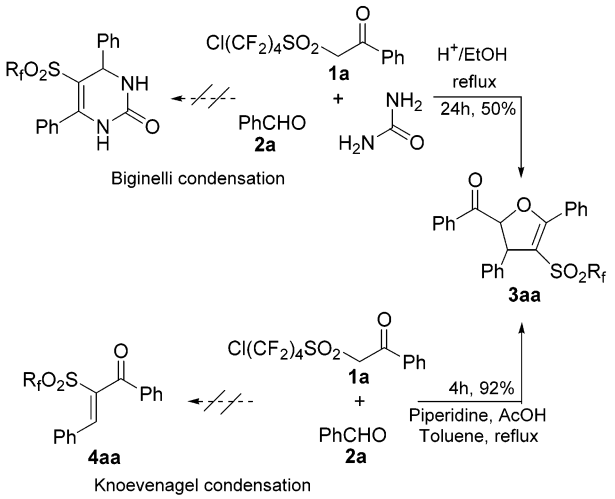
(6) Calo, V.; Scordari, F.; Nacci, A.; Schingaro, E.; D'Accolti, L.; Monopoli, A. *J. Org. Chem.* **2003**, *68*, 4406.

(7) (a) Bose, D. S.; Fatima, L.; Mereyala, H. B. *J. Org. Chem.* **2003**, *68*, 587. (b) Saloutin, V. I.; Burgart, Y. V.; Kuzueva, O. G.; Kappe, C. O.; Chupakhin, O. N. *J. Fluorine Chem.* **2000**, *103*, 17.

(8) For synthetic methods of substituted dihydrofuran derivatives, see: (a) Antonioletti, R.; Malancona, S.; Bovicelli, P. *Tetrahedron* **2002**, *58*, 8825. (b) Jiang, Y.; Ma, D. *Tetrahedron: Asymmetry* **2002**, *13*, 1033. (c) Carrido, J. L.; Alonso, I.; Carretero, J. C. *J. Org. Chem.* **1998**, *63*, 9406. (d) Hagiwara, H.; Sato, K.; Nishino, D.; Hoshi, T.; Suzuki, T.; Ando, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2946. (e) Wang, Y. L.; Zhu, S. Z. *Tetrahedron* **2001**, *57*, 3383. (f) Melikyan, G. G.; Vostrowsky, O.; Bauer, W.; Bestmann, H. J.; Khan, M.; Nicholas, K. M. *J. Org. Chem.* **1994**, *59*, 222.

10.1021/jo049317y CCC: $27.50
Published on Web 08/19/2004

SCHEME 3



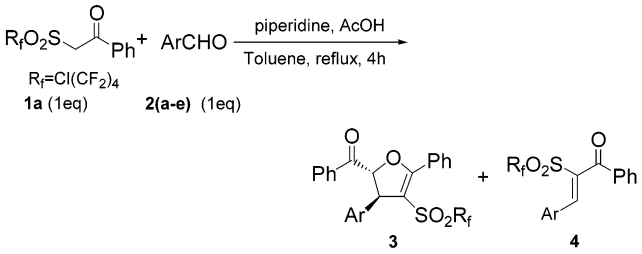
We found that **3aa** could also be isolated as the sole product in 92% yield when **1a** was reacted with **2a** under Knoevenagel condensation conditions, but the expected Knoevenagel condensation product, 2-(4-chloro-1,1,2,2,3,3,4,4-octafluorobutane-1-sulfonyl)-1,3-diphenyl-propenone **4aa**, was not detected (Scheme 3). It was obvious that this reaction is different from the reaction of β-keto aryl sulfones or α-perfluoroalkanesulfonyl acetate esters (Scheme 1).

The five-membered heterocyclic structure of **3aa** was further established by single-crystal X-ray diffraction analysis,[9,10] which indicated a trans conformation between the aryl (Ph, C-25) and the benzoyl (PhCO, C-26) groups. Moreover, the coupling constant between the C-25 proton and the C-26 proton was 3.0 Hz in the ^{1}H NMR of **3aa**, which also confirmed the trans conformation.[8c,d]

To explore the scope of this reaction, we investigated a variety of substituted aromatic aldehydes under Knoevenagel condensation conditions. As shown in Table 1, benzaldehyde (**2a**), 4-bromobenzaldehyde (**2b**), and 4-nitrobenzaldehyde (**2c**) reacted with **1a** and produced tetrasubstituted 2,3-dihydrofuran as the sole product in high yield (Table 1, entries 1−3). With an aldehyde bearing an electron-donating group, such as **2d**, two products, **3ad** and **4ad** (the Knoevenagel product), were obtained in a ratio of 3:2. These could not be fully separated due to their similar polarity (Table 1, entry 4). Another electron-rich aldehyde, **2e**, gave a similar result (Table 1, entry 5).

In further studies, it was found that piperidine is crucial in this reaction process, and acetic acid is unnecessary. When the product mixture of **3** and **4** was treated with **1a** and piperidine in toluene, the Knoevenagel product, **4**, was transformed completely to a dihydrofuran derivative **3** (Scheme 4). On the basis of these facts, it is concluded that **4** is the intermediate

TABLE 1. Reaction of 1a with Aromatic Aldehydes under Knoevenagel Condensation Conditions



entry	Ar in **2**	product[c]	ratio[d]	yield[a] (%)
1	C_6H_5 (**2a**)	**3aa**		92
2	*p*-BrC_6H_4 (**2b**)	**3ab**		94
3[b]	*p*-$NO_2C_6H_4$ (**2c**)	**3ac**		95
4	*p*-$CH_3C_6H_4$ (**2d**)	**3ad** + **4ad**[11]	3:2	
5	*p*-$CH_3OC_6H_4$ (**2e**)	**3ae** + **4ae**[11]	4:5	

[a] Isolated yield based on **1a**. [b] **1a/2c** 1:0.6 (equiv). [c] **3ad** and **4ad**, **3ae** and **4ae** could not be separated by column chromatography. [d] Determined by ^{1}H NMR.

SCHEME 4

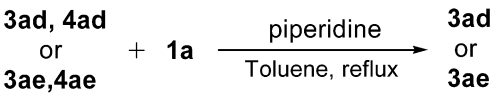
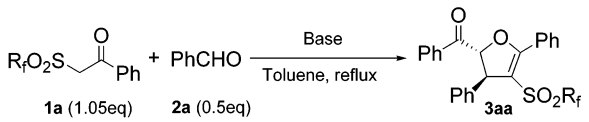


TABLE 2. Catalytic Activity of Different Amines in the Model Reaction



entry	base (equiv)	time (h)	yield[a] (%)
1	piperidine(0.2)	5	86
2	piperidine(1)	1	84
3	Et_3N(1)	2	84
4	$PhCH_2NH_2$(1)	1	trace[b]
5	$PhNH_2$(1)	1	

[a] Isolated yield based on **2a**. [b] Not isolated.

product which reacts further with an additional 1 equiv of **1a** to yield the final product **3**. If piperidine was replaced by inorganic alkalis, such as K_2CO_3, NaOH, NaH, etc., no reaction occurred. It could be explained by their poor solubility in toluene.

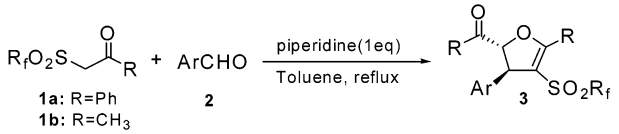
The catalytic activity of different amines was investigated (Table 2). We found that increasing piperidine to 1 equiv (based on **1a**) accelerated the reaction (Table 2, entry 2). Triethylamine can also catalyze this reaction well except for appreciably longer reaction times (Table 2, entry 3). However, aniline and benzylamine, the weaker bases, have little catalytic activity (Table 2, entries 4 and 5). Under the optimized reaction conditions (1 equiv of piperidine), we synthesized a series of tetrasubstituted 2,3-dihydrofuran derivatives. All of these results are listed in Table 3.

(9) Crystal data for compound **3aa**: $C_{27}H_{17}ClF_8O_4S$, MW = 624.92, monoclinic, *P*2[1]/*C*, Mo Kα, final *R* indices [$I > 2\sigma(I)$], $R_1 = 0.1086$, $wR_2 = 0.2887$, $a = 12.689(3)$ Å, $b = 11.775(2)$ Å, $c = 19.050(4)$ Å, $\alpha = 90°$, $\beta = 104.04°$, $\gamma = 90°$, $V = 2761.3(10)$ Å^3, $T = 293(2)$ K, $Z = 4$, reflections collected/unique: 7878/6341 ($R_{int} = 0.0357$), no observation [$I > 2\sigma(I)$] 4004, parameters 372.

(10) The bond length of C23−C24 is 1.363 Å, which shows the double-bonded character; the bond length of C25−C26 is 1.556 Å.

(11) We synthesized **4ad** and **4ae** by another method. ^{1}H NMR data (300 MHz, $CDCl_3$): **4ad** δ 8.08 (1H, s), 7.95 (2H, d, $J = 7.5$ Hz), 7.27−7.62 (5H, m), 7.11 (2H, d, $J = 8.1$ Hz), 2.32 (3H, s); **4ae** δ 8.04 (1H, s), 7.96 (2H, d, $J = 7.2$ Hz), 7.36−7.59 (5H, m), 6.79 (2H, d, $J = 8.7$ Hz), 3.77 (3H, s). Other spectral data will be reported in detail. Manuscript in preparation.

TABLE 3. Synthesis of Tetrasubstituted *trans*-2,3-Dihydrofurans[a]



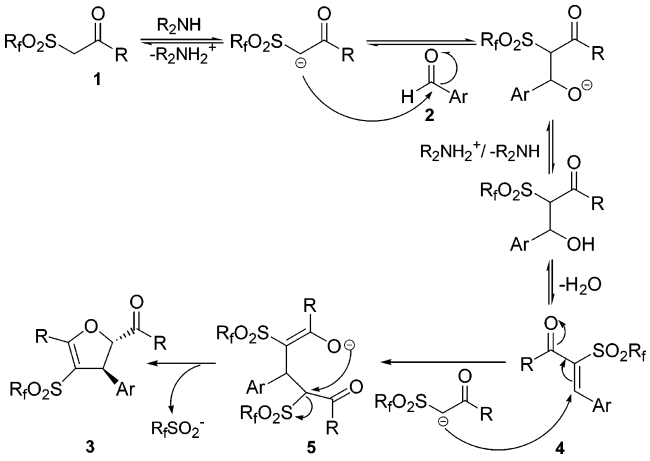
entry	1	Ar in **2**	time (h)	product	yield[b] (%)
1	**1a**	C_6H_5 (**2a**)	1	**3aa**	84
2	**1a**	*p*-BrC_6H_4 (**2b**)	1	**3ab**	87
3	**1a**	*p*-$NO_2C_6H_4$ (**2c**)	1	**3ac**	90
4	**1a**	*p*- $CH_3C_6H_4$ (**2d**)	1.5	**3ad**	78
5	**1a**	*p*-$CH_3OC_6H_4$ (**2e**)	1.5	**3ae**	80
6	**1a**	*p*-ClC_6H_4 (**2f**)	1	**3af**	85
7	**1a**	*m*-ClC_6H_4 (**2g**)	1	**3ag**	88
8	**1a**	*o*-ClC_6H_4 (**2h**)	1.5	**3ah**	82
9	**1a**	4-pyridyl (**2j**)	1	**3aj**	85
10	**1b**	C_6H_5 (**2a**)	3	**3ba**	70
11	**1b**	*p*-$NO_2C_6H_4$ (**2c**)	0.5	**3bc**	92
12	**1b**	*p*-$CH_3C_6H_4$ (**2d**)	3	**3bd**	72
13	**1b**	2-furyl (**2i**)	10	**3bi**	54

[a] **1:2** 1.05:0.5 (equiv). [b] Isolated yield based on aldehydes.

A possible mechanism similar to that reported by Calo et al.[6] is shown in Scheme 5. First, the reaction of **1** with **2** gives the Knoevenagel condensation product α-polyfluoroalkanesulfonyl-α,*β*-unsaturated ketone **4** as the intermediate. Compound **4** could be a better electrophilic Michael acceptor than α-polyfluoroalkanesulfonyl-α,*β*-unsaturated esters. The newly formed carbon−carbon double bond is readily attacked by the anion of **1**. Then, a Michael addition affords the enolate anion **5**. Finally, the subsequent intramolecular nucleophilic displacement of **5** gave the cycloadduct **3**. During ring closure, the two large neighboring groups (Ar and ArCO) preferably formed trans conformation for the sake of stereohindrance.

In summary, we have found that the reaction of *β*-keto polyfluoroalkanesulfones with aldehydes is different from the traditional Knoevenagel condensation reaction. This reaction proceeds past the initial condensation product to provide an efficient and novel method for the stereoselective synthesis of fluorine-containing tetrasubstituted *trans*-2,3-dihydrofurans. A rational reaction mechanism is presented. Further studies for application of this methodology are ongoing in our laboratory.

SCHEME 5



Experimental Section

General Procedure for the Synthesis of Tetrasubstituted *trans*-2,3-Dihydrofurans. A mixture of $ClC_4F_8SO_2CH_2$-COPh **1a** (356 mg, 0.84 mmol), benzaldehyde **2a** (43 mg, 0.4 mmol), and piperidine (0.078 mL, 0.8 mmol) in toluene (16 mL) was heated at reflux for 1 h with azeotropic removal of water using a Dean−Stark trap. TLC analysis indicated the reaction was completed. The mixture was cooled to room temperature, the solvent was removed under reduced pressure, and chromatography (SiO_2, hexane/ethyl ether, 10:1) afforded **3aa** (213 mg, 84%).

Acknowledgment. This work is dedicated to Professor Li-Xin Dai on the occasion of his 80th birthday. Financial support of this work by the National Science Foundation of China is gratefully acknowledged (Nos. 20032010, 20372077).

Supporting Information Available: General experimental method, spectral data of compounds **3aa**−**3bi**, **and** X-ray crystallographic files for **3aa**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO049317Y