Tetrahedron Letters 52 (2011) 6619–6622

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

2-Oxo-2-polyfluoroalkylethane-1-sulfones and -sulfamides in the Biginelli and 'retro-Biginelli' reactions

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ARTICLE INFO

Article history:
Received 28 July 2011
Revised 12 September 2011
Accepted 30 September 2011
Available online 6 October 2011

Keywords:
Biginelli reaction
Tetrahydropyrimidinone
Polyfluoroalkyl
Ketosulfone
Ketosulfamide
Hexamethylenetetramine

ABSTRACT

2-Oxo-2-polyfluoroalkylethane-1-sulfones and -sulfamides react with aryl aldehydes and urea under Biginelli reaction conditions to yield 4-hydroxy-4-polyfluoroalkyl-5-sulfonyl-6-aryl-tetrahydropyrimidinones. The latter compounds on reaction with hexamethylenetetramine (HMTA) under thermal conditions undergo 'retro-Biginelli' reaction involving replacement of the 6-aryl substituent of the pyrimidinone cycle with a hydrogen atom donated by HMTA. Hexamethylenetetramine was employed for the first time in place of formaldehyde in the reported one-step Biginelli protocol for the synthesis of fluorinated sulfonyl-containing 6-unsubstituted tetrahydropyrimidinones.

Multicomponent reactions are powerful synthetic tools in organic chemistry allowing the construction of complex heterocyclic compounds from several simple functional substrates in a one-pot procedure.[1] The Biginelli reaction represents a widely studied three-component condensation which provides an easy and economic route to a pyrimidine core.[2] Interest in this reaction has been rekindled because of the pharmaceutical applications of the products formed.[3] A large variety of β-dicarbonyl compounds as well as diverse catalysts have been tested in the Biginelli procedure,[2c] but attention on this topic persists.

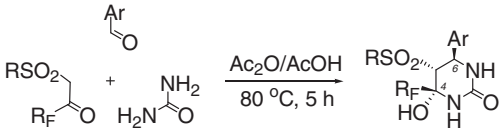
In this Letter we report on the application of 2-oxo-2-polyfluoroalkylethane-1-sulfones and -sulfamides as β-dicarbonyl surrogates in the Biginelli reaction for the preparation of pyrimidinones substituted with a sulfonyl or sulfamide moiety. The products underwent a 'retro-Biginelli' reaction when treated with hexamethylenetetramine (HMTA).

We found that 2-oxo-2-polyfluoroalkylethane-1-sulfones **1a,b** and -sulfamides **1c**,**d** underwent a three-component reaction with aryl aldehydes and urea to give the expected substituted tetrahydropyrimidinones **2a–h** (Table 1). In our case, 4-hydroxy-containing pyrimidinones were formed, similarly to the Biginelli reaction of related fluoroalkyl keto compounds described in the literature.[4]

Favorable reaction conditions involved heating the starting compounds in a mixture of acetic anhydride and acetic acid as solvent. The use of acetic anhydride derived from the necessity to trap water, evolved during the condensation, because the starting polyfluoroalkyl keto compounds easily form hydrates and become unreactive.

Compounds **2** were isolated as single diastereomers in 70–85% yields.[5] Their stereochemistry was deduced from NMR data and by comparison with the data of other reported similar compounds.[4a,b]

Table 1
Biginelli reaction of 2-oxo-2-polyfluoroalkylethane-1-sulfones **1a**,**b** and -sulfamides **1c**,**d**



1a-d **2a-h**

Ketone	R_F	R	Ar	Product	Yield[a] (%)
1a	CF_3	*p*-Tol	Ph	**2a**	85
1a	CF_3	*p*-Tol	*p*-$MeOC_6H_4$	**2b**	74
1b	HCF_2CF_2	*p*-Tol	Ph	**2c**	77
1b	HCF_2CF_2	*p*-Tol	*p*-$MeOC_6H_4$	**2d**	70
1c	CF_3	Et_2N	Ph	**2e**	76
1c	CF_3	Et_2N	*p*-$MeOC_6H_4$	**2f**	82
1d	HCF_2CF_2	Et_2N	Ph	**2g**	72
1d	HCF_2CF_2	Et_2N	*p*-$MeOC_6H_4$	**2h**	70

[a] Isolated yield.

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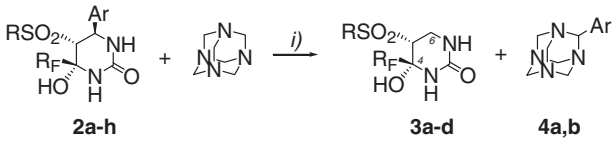
doi:10.1016/j.tetlet.2011.09.143



3: $R_F = CF_3$, R = *p*-Tol (**a**); $R_F = HCF_2CF_2$, R = *p*-Tol (**b**);
$R_F = CF_3$, R = Et_2N (**c**); $R_F = HCF_2CF_2$, R = Et_2N (**d**);
4: Ar = Ph (**a**); *p*-MeO-C_6H_4 (**b**)

Scheme 1. Reagents and conditions: (i) $PhCH_3$, reflux, 5 h.

Our further efforts were directed to the dehydration of hydroxy derivatives **2** to give dihydropyrimidinones which are classical Biginelli products from the condensation of nonfluorinated keto compounds.[2a] The use of *p*-toluenesulfonic acid, a known dehydrating agent for compounds of this type,[4a] led to no results. We tested several different dehydrating agents but our attempts proved unsuccessful. During the search for methods to modify our synthesized Biginelli products we serendipitously found that heating compound **2a** with HMTA in a solvent led to tetrahydropyrimidinone **3a** which did not contain an aryl substituent at C-6 of the heterocyclic framework. We examined this unprecedented transformation more carefully and found that it was general for all our fluorinated tetrahydropyrimidinones **2** bearing both sulfonyl and sulfamide moieties. The optimal conditions for this transformation were refluxing a suspension of equimolar amounts of reactants in toluene. After separation of solid compounds **3** the mother liquor was evaporated, and after purification of the residue by chromatography on silica gel, we obtained the other product of this reaction, compound **4** (Scheme 1). The reaction also takes place in refluxing acetonitrile, but in this case more careful purification of the final products was required and the yields of **3** were lower.

The stereochemistry of tetrahydropyrimidinone **3a** was determined by X-ray diffraction (Fig. 1).[6] The structures of derivatives **3b–d** were supported by NMR data; their spectroscopic characteristics were similar to those of compound **3a**.[7] The ^{1}H NMR spectra of the substituted hexamines **4** displayed similar sets of signals, two AB systems due to the four methylene groups, a singlet for the fifth CH_2-group and a singlet resulting from the CH–Ar proton.[7]

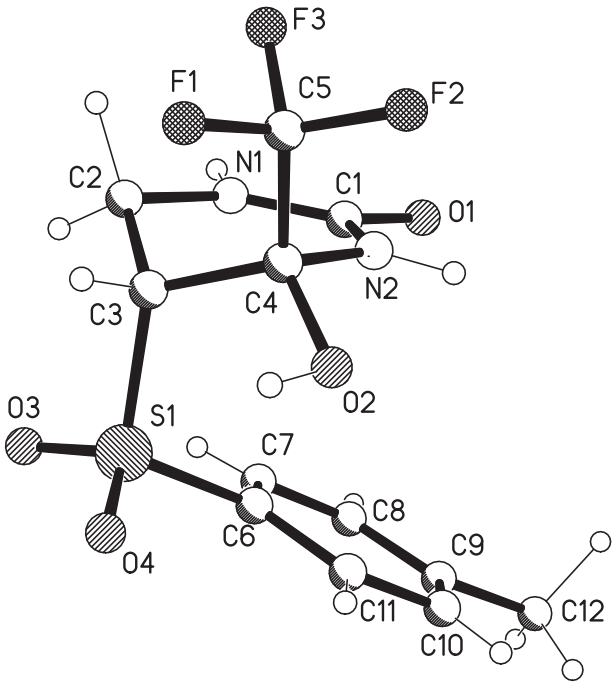


Figure 1. X-ray crystal structure of **3a**.

Compounds **4a,b** were isolated as viscous oils and were soluble in polar solvents such as chloroform, acetonitrile, and ethanol. They appeared unstable in $CDCl_3$ solution and over 1–2 days underwent partial conversion into an aryl aldehyde and HMTA according to the ^{1}H NMR data. This transformation is probably induced by the acidic chloroform, since acidification of a chloroform solution of **4a** with 35% hydrochloric acid in an NMR tube caused complete decomposition into benzaldehyde and HMTA as was evident from the ^{1}H NMR spectrum. This instability of compounds **4** explains their low isolated yields (20% for **4a** and 16% for **4b**) but their isolation and characterization are useful for clarification of the outcome of this retro-reaction.

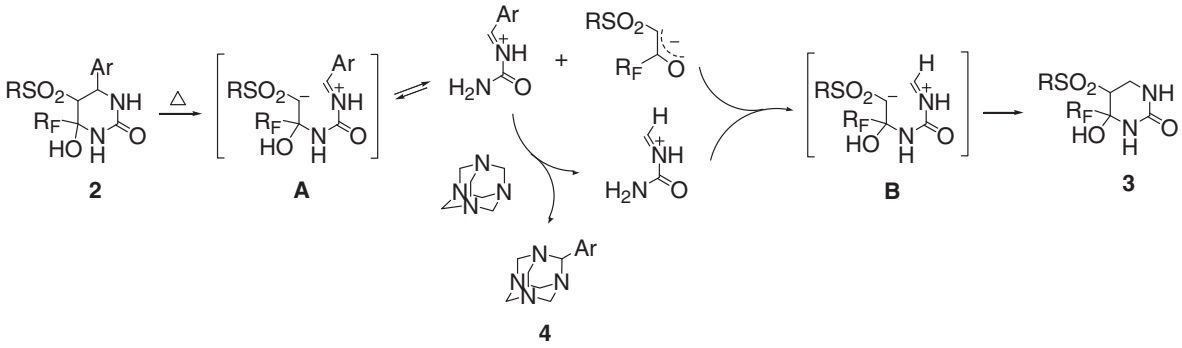
As can be seen from the mechanism proposed in Scheme 2, formal displacement of the aryl substituent at C-6 of the tetrahydropyrimidinone **2** by a hydrogen atom, donated from a molecule of the hexamine, occurs. The aryl group in turn is transferred to the hexamine to give the 2-aryl substituted derivative. We assume that the formation of **3** proceeds through acyclic intermediate **A**, generated via thermal cleavage of the pyrimidinone core in **2**. In this intermediate the carbanion adjacent to the sulfonyl substituent is stabilized by the presence of a strong electron-withdrawing group, while the iminium cation is postulated as an intermediate in the condensation of aldehydes with urea in the course of the classical Biginelli reaction. The arylidene group is transferred to HMTA releasing the methylidene moiety to afford the intermediate **B**, subsequent cyclization of which results in the 6-unsubstituted tetrahydropyrimidinone **3**.

We have found that the above-mentioned transformation only occurs on heating and does not proceed at room temperature. No intermediates were detected by monitoring the reaction by NMR. We observed either a mixture of the initial tetrahydropyrimidinone **2** and HMTA with no final products after 1–1.5 h or a mixture of **2**, **3**, **4** and HMTA after a longer period and, finally, full conversion of **2** into **3**.

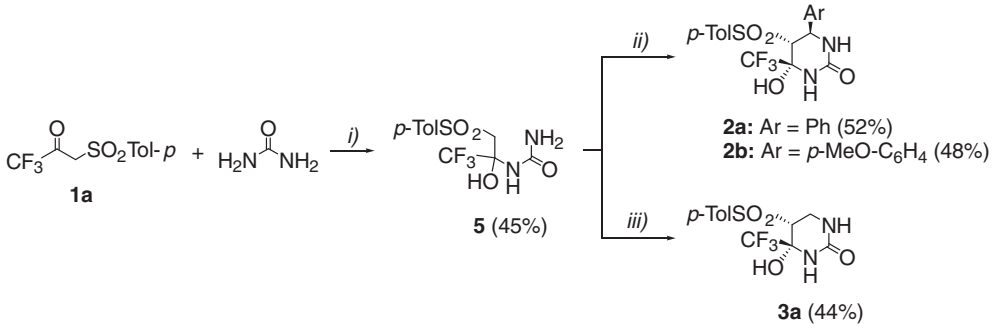
In attempts to support the proposed assumption concerning the mechanistic features of the described retro-reaction we synthesized adduct **5** by reaction of ketosulfone **1a** with urea in CH_3CN and then reacted it with several aryl aldehydes and with HMTA (Scheme 3).

The adduct **5** was a crystalline compound isolated in 45% yield[8] because only 50% conversion of the ketosulfone **1a** was achieved in the reaction with urea. However isolation of this adduct as an individual compound and its subsequent reactions with aldehydes and with HMTA yielding tetrahydropyrimidinones **2a,b** and **3a** serves as an additional argument in support of the suggested pathway for the retro-reaction. Moreover, this adduct can be considered as a possible intermediate in the Biginelli condensation of polyfluoroalkyl keto derivatives. A number of mechanisms have been proposed for the Biginelli reaction, and recently[9] it was shown that an iminium pathway, consisting of initial condensation of an aldehyde with urea in acidic media followed by addition of the enol form of the ketone to the resulting iminium ion, is the most favorable. In our case, the product of initial addition of urea to the highly electrophilic C=O group of the fluoroalkyl ketones, adduct **5**, is acidic enough to promote the final cyclization into the pyrimidinone in reactions with aldehydes or with HMTA. The Biginelli reaction sequence, involving the initial condensation of urea with acetoacetate, supported by isolation of the corresponding intermediate (enamine pathway), was also proposed for the nonfluorinated series.[10]

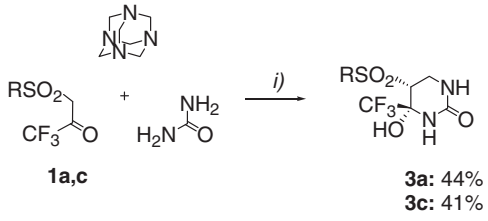
The reaction of **5** with hexamethylenetetramine led us to anticipate that HMTA can be used in the Biginelli condensation as a



Scheme 2. Proposed 'retro-Biginelli' reaction pathway.



Scheme 3. Reagents and conditions: (i) CH_3CN, reflux, 2 h; (ii) ArCHO, CH_3CN, rt, 8 h; (iii) HMTA, CH_3CN, rt, 8 h.



Scheme 4. Reagents and conditions: (i) TMSCl (cat.), CH_3CN, reflux, 3 h, ratio of **1**-HMTA–urea–TMSCl = 1:0.5:1:0.2.

masked equivalent of formaldehyde for the synthesis of 6-unsubstituted pyrimidinones of type **3**. Only a few publications report on the effective utilization of formaldehyde[11] or its carbonyl equivalents (1,3-oxazinanes as masked formaldehyde)[12] in Biginelli condensations to prepare dihydropyrimidinones. Our attempts to use paraformaldehyde and urea together with trifluoromethyl ketosulfone **1a** as a model substrate in the acid-catalyzed Biginelli condensation in order to obtain the desired pyrimidinone proved fruitless, the reactions being accompanied with the formation of undefined complex mixtures. HMTA is known to be a formylating agent in a number of organic reactions, but has never been utilized in the multicomponent Biginelli synthesis instead of formaldehyde, therefore, the use of HMTA in this reaction seemed promising. Indeed, when ketones **1a,c** were subjected to the Biginelli reaction with urea and HMTA we obtained the expected tetrahydropyrimidinones **3a,c** (Scheme 4).

The reactions of **1a,c** with HMTA and urea proceeded under reflux in acetonitrile over 3 h. Catalytic amounts of TMSCl were used to accelerate the cyclocondensation, however, we found that the reaction could proceed without any catalyst, thus it is self-catalyzed. Tetrahydropyrimidinone **3a** precipitated from the reaction mixture whereas compound **3c** was obtained after removal of the solvent and recrystallization.

In conclusion, we have found that 4-hydroxy-4-polyfluoroalkyl-5-tolylsulfonyl(diethylsulfamido)-6-aryl-tetrahydropyrimidin-2(1*H*)-ones, obtained via Biginelli condensation of 2-oxo-2-polyfluoroalkylethane-1-sulfones and -sulfamides with aryl aldehydes and urea, undergo a 'retro-Biginelli' reaction to give 6-unsubstituted tetrahydropyrimidin-2(1*H*)-ones on heating with hexamethylenetetramine. We have also demonstrated for the first time that HMTA can be used in Biginelli reactions as a masked form of formaldehyde providing direct access to 6-unsubstituted tetrahydropyrimidin-2(1*H*)-ones.

Acknowledgment

We thank Dr. V. V. Trachevsky, Common Usage Center of Radiospectroscopy, NAS of Ukraine, Kyiv for recording the NMR spectra.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.09.143.

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5. For selected data and the data for other procedures and compounds, see: Supplementary data.
General procedure for the Biginelli reaction of 2-oxo-2-polyfluoroalkylethane-1-sulfones **1a**,**b** *and -sulfamides* **1c**,**d**. *Preparation of* **2a**–**h**: To a mixture of urea (66 mg, 1.1 mmol) and the corresponding aryl aldehyde (1.1 mmol), a solution of ketosulfone **1a**,**b** (1 mmol) or ketosulfamide **1c**,**d** (1 mmol) in a mixture of Ac_2O (1.5 ml, 1.5 mmol) and glacial AcOH (1 ml) was added. The mixture was heated at 80 °C for 5 h, allowed to cool, diluted with Et_2O (2 ml) and the precipitate filtered, washed with H_2O, Et_2O, and dried to give tetrahydropyrimidinones **2a**–**h** as colourless or white solids which were crystallized from an appropriate solvent. *Analytical data for compound* **2a**. Yield 0.35 g (85%), mp 206 °C (CH_3CN). Colourless cubes. IR (KBr): 3420, 3350, 3240, 3100, 1690 (C=O). ^{19}F NMR (DMSO-d_6, 188 MHz): δ −83.05 (3F, s, CF_3). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.40 and 7.88 (4H, dd, J = 8.1 Hz, C_6H_4-*para*), 7.64 (2H, m, NH-1 + OH), 7.27–7.37 (5H, m, C_6H_5), 6.96 (1H, s, NH-3), 5.47 (1H, d, J = 4.5 Hz, H-6), 4.16 (1H, s, H-5), 2.41 (3H, s, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 153.95 (s, C=O), 144.07 (s, C_{Ar}-CH_3), 140.57 (s, C_{Ph}-*ipso*), 138.00 (s, C_{Ar}-SO_2), 129.28, 128.86, 128.37, 127.24 (s, 4C_{Ar}-H), 125.58 (s, C_{Ar}-*ortho*), 122.39 (q, J_{CF} = 285.4 Hz, CF_3), 80.90 (q, $^2J_{CF}$ = 33.0 Hz, C-4), 66.05 (s, C-5), 49.76 (s, C-6), 21.12 (s, CH_3). MS APCI (m/z): 415 ([M+H]$^+$, 100%). Anal. Calcd for $C_{18}H_{17}F_3N_2O_4S$: C, 52.17; H, 4.13; N, 6.76; S, 7.74. Found: C, 52.11; H, 4.16; N, 6.89; S, 7.83.
6. *Selected X-ray crystallographic data for compound* **3a**: $C_{12}H_{13}F_3N_2O_4S$, monoclinic, a = 21.411(5) Å, b = 6.8914(17) Å, c = 21.721(6) Å, β = 116.923(7), V = 2857.7(13) Å^3, space group $C2/c$. CCDC-749283 contains the Supplementary crystallographic data for the structure reported in this Letter. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.
7. *Compounds* **3a**–**d** *and* **4a**,**b**. *General procedure*: A suspension of tetrahydropyrimidinone **2a**–**h** (1.0 mmol) and hexamethylenetetramine (140 mg, 1.0 mmol) in toluene (3 ml) was refluxed at 110 °C for 5 h. After cooling to room temperature the resulting solid was filtered, washed with hot H_2O then cold acetone and dried to give pure compounds **3a**–**d**. The mother liquor, after filtration of compounds **3a**–**d**, was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel giving **4a**,**b**. *Analytical data for compound* **3a**. Yield 0.25 g (75%) from **2a**, mp 240–242 °C (1,4-dioxane–H_2O). Colourless solid. IR (KBr): 3380, 3230, 3090, 2950, 2910, 1710 (C=O). ^{19}F NMR (DMSO-d_6, 188 MHz): δ −82.48 (3F, s, CF_3). ^{1}H NMR (DMSO-d_6, 100 MHz): δ 7.44, 7.02, 6.72 (3H, s, 2NH + OH), 7.40 and 7.80 (4H, dd, J = 8.4 Hz, C_6H_4-*para*), 4.17 (1H, m, H-5), 3.81 (1H, ABm, J_{AB} = 14.4 Hz, H_A-6), 3.36 (1H, ABd, J_{AB} = 14.4 Hz, J = 3.3 Hz, H_B-6), 2.40 (3H, s, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 153.02 (s, C=O), 143.82 (s, C_{Ar}-CH_3), 137.85 (s, C_{Ar}-SO_2), 129.06, 128.34, (s, 2C_{Ar}-H), 122.43 (q, J_{CF} = 288.5 Hz, CF_3), 80.92 (q, $^2J_{CF}$ = 30.1 Hz, C-4), 58.21 (s, C-5), 36.30 (s, C-6), 20.80 (s, CH_3). MS APCI (m/z): 339 ([M+H]$^+$, 100%). Anal. Calcd for $C_{12}H_{13}F_3N_2O_4S$: C, 42.60; H, 3.87; N, 8.28; S, 9.48. Found: C, 42.50; H, 3.95; N, 8.50; S 9.60. *Analytical data for compound* **4a**. Yield 43 mg (20%) from **2a** (eluent MeOH–CH_2Cl_2, 1:1, R_f = 0.50). Yellowish oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37–7.53 (5H, m, C_6H_5), 5.65 (1H, s, H-2), 4.90 (2H, AB, J_{AB} = 12.4 Hz, CH_AH_B), 5.01 (2H, J_{AB} = 12.4 Hz, CH_AH_B), 4.78 s (2H, H-6), 4.65 (2H, AB, J_{AB} = 12.8 Hz, CH_AH_B), 4.50 (2H, AB, J_{AB} = 12.8 Hz, CH_AH_B). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.18 (s, C_{Ph}-*ipso*), 128.95, 127.86, 126.43 (s, 3C_{Ph}), 79.79 (s, C-2), 76.49 (s, 2CH_2), 74.52 (s, 2CH_2), 68.40 (s, C-5). GC/MS (m/z): 216 (M$^+$, 21%), 118 (100%), 91 (52%), 42 (75%). Anal. Calcd for $C_{12}H_{16}N_4$: C, 66.64; H, 7.46; N, 25.90. Found: C, 66.34; H, 7.60; N, 25.75.
8. *Compound* **5**: A mixture of ketosulfone **1a** (133 mg, 0.5 mmol) and urea (30 mg, 0.5 mmol) in acetonitrile (2 ml) was stirred under reflux for 2 h. After cooling the yellow solution to room temperature, unreacted urea crystallized and was removed by filtration. The mother liquor was evaporated under vacuum, and the viscous oil in the residue was treated with Et_2O to form a white solid which was filtered and dried to give compound **5**. Yield 73 mg (45%), mp 92 °C with decomposition. ^{19}F NMR (DMSO-d_6, 188 MHz): δ −83.97 (3F, s, CF_3). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.99 (1H, br s, NH), 7.41 and 7.78 (4H, dd, J = 8.4 Hz, C_6H_4-*para*), 7.32 (1H, s, OH), 6.22 (2H, br s, NH_2), 3.92 (2H, s, CH_2), 2.39 (3H, s, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 159.73 (s, C=O), 144.31 (s, C_{Ar}-CH_3), 138.37 (s, C_{Ar}-SO_2), 129.57, 128.12 (s, 2C_{Ar}-H), 123.31 (q, J_{CF} = 293.4 Hz, CF_3), 82.06 (q, $^2J_{CF}$ = 31.2 Hz, C-4), 56.25 (s, CH_2), 21.19 (s, CH_3). MS APCI (m/z): 327 ([M+H]$^+$, 100%). Anal. Calcd for $C_{11}H_{13}F_3N_2O_4S$: C, 40.49; H, 4.02; N, 8.59; S, 9.83. Found: C, 40.63; H, 4.12; N, 8.69; S, 9.90.

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