Unexpected Formation of Fluorine-Containing Multiply Substituted Dispirocyclohexanes from the Reaction of Ethyl-4,4,4-trifluoro-1,3-dioxobutanoate and 2-Arylideneindane-1,3-diones

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Abstract: In the presence of a catalytic amount of piperidine (10 mol%), reaction of ethyl 4,4,4-trifluoro-3-oxobutanoate **3** and 2-arylidene-indane-1,3-diones **4** gave the unexpected fluorine-containing multiply substituted dispirocyclohexanes **5** in good yields. The structures of compounds **5** were fully confirmed by spectroscopic methods and elemental analysis. A representative compound **5a** was further confirmed by XRD analysis. A plausible reaction mechanism for the formation of compounds **5** was presented.

Key words: fluorine-containing, spiro compound, polysubstitution, 2-arylidene-indan-1,3-dione, ethyl 4,4,4-trifluoro-3-oxobutanoate

It is now well established that introduction of fluorine atoms or fluoroalkyl moieties into organic substrates gives rise to important physicochemical modifications of the concerned molecules.[1] Such specific properties have found applications in various fields.[2] For example, the introduction of fluorine atoms or fluoroalkyl groups into molecules constitutes a classical and systematic modification of biological properties used in medicinal chemistry for the design of new drugs.[3] More specifically, fluoroalkyl groups (particularly the CF_3 group) cause a great interest since they generally increase the lipophilicity of the compounds and, usually, enhance their bioactive ability. Consequently, more fluoroalkylated molecules find application in the pharmaceutical fields.[4] On the other hand, spiro compounds represent an important class of naturally occurring substances characterized by highly pronounced biological properties.[5] Due to these observations, fluoroalkylated spirocyclic molecules should be valuable building blocks to construct medicinally relevant complex structures.

2-Arylidene-indane-1,3-diones are highly reactive 1,1-diactivated alkenes that have been used extensively as acceptors in 1,4-addition of a variety nucleophiles[6] or in 1,3-dipolar cycloaddition,[7] as dienophile[8] and diene[9] in Diels–Alder reactions, respectively, and as versatile synthons in other reactions,[10] especially in the fields of medical and materials chemistry.[11] More recently, the reactions involving 2-arylidene-indane-1,3-diones or 1,3-indanedione as reaction substrates are studied extensively.[12]

In order to continue our ongoing research on the synthesis of fluorine-containing compounds based on trifluoromethyl-1,3-dicarbonyl compound, a versatile fluorine-containing building block,[13] herein, we wish to report the unexpected formation of fluorine-containing multiply substituted dispirocyclohexanes from the reaction of ethyl-4,4,4-trifluoro-1,3-dioxobutanoate and 2-arylidene-indane-1,3-diones.

In an initial endeavor, we carried out the reaction of ethyl-4,4,4-trifluoro-1,3-dioxobutanoate and 2-benzylidene-indane-1,3-diones in the molar ratio of 1:1 in the presence of a catalytic amount of triethylamine (20%) in ethanol at room temperature. However, no reaction occurred. Subsequently, the catalyst was changed to a catalytic amount of piperidine (20%). TLC analysis showed that a new compound was formed, however, ethyl-4,4,4-trifluoro-1,3-dioxobutanoate did not react completely. Surprisingly, according to the ^1H NMR spectrum of newly formed product, it was clear that two molecules of 2-arylidene-indane-1,3-diones, derived from the Knoevenagel condensation of aromatic aldehyde and 1,3-indanedione under solvent-free conditions,[14] were involved in the reaction. Thus, the molar ratio of ethyl-4,4,4-trifluoro-1,3-dioxobutanoate to 2-benzylidene-indane-1,3-diones was modified to 1:2, and the reaction was carried out under the same reaction conditions. After stirring 12 hours at room temperature, TLC showed that the reaction proceeded smoothly and general workup afforded the product **5a** in 47% yield (Scheme 1).

Based on the results above, the reaction conditions were optimized to improve the yield by changing the base and solvent used. The effect of organic bases on the reaction efficiency and yield was firstly screened (Table 1). The reactions did not occur either in the absence of base catalyst or in the presence of a catalytic amount of other organic bases such as pyridine, Et_3N, and DBU even with a prolonged reaction time (24 h; entries 1–4, Table 1). The reactions gave the product **5a** in 59% and 53% yields under the catalysis of DMAP and DABCO, respectively. It was obvious that piperidine (entries 7–10, Table 1) demonstrated superior catalytic activity and was the best catalyst among those examined. Use of 10 mol% of piperidine

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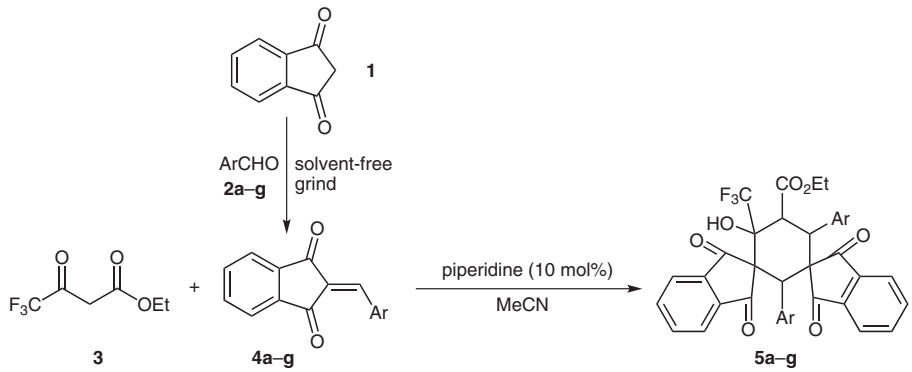

Scheme 1 Reaction of ethyl-4,4,4-trifluoro-1,3-dioxobutanoate **3** with 2-benzylidene-indane-1,3-diones **4**

was sufficient to push the reaction forward but 5 mol% of piperidine was not enough (entries 7 and 8, Table 1). Higher amounts of the catalyst did not further improve the yield of product **5a** (entries 9 and 10, Table 1).

The solvent effect was the next considered factor. As shown in Table 1, the reactions gave the better yield in polar aprotic solvents such as MeCN and CH_2Cl_2 than that in protic solvents such as EtOH or MeOH (entries 8, 11–13, Table 1).

With the optimal results in hand as shown in entry 8 (Table 1), we investigated the scope and limitation of the reaction with a variety of 2-arylidene-indane-1,3-diones. The reaction results were summarized in Table 2. It was clear that the product yield was influenced by both electronic and steric effects of the substituting groups on the phenyl ring in the 2-arylidene-indane-1,3-diones. We observed that when 2-arylidene-indane-1,3-diones with strong electron-donating group on the phenyl ring was employed as the reaction substrates, the reaction did not afford the corresponding products (entry 8 and 9, Table 2). Moreover, the effect of steric hindrance on the phenyl ring of 2-arylidene-indane-1,3-dione was also noticeable. Hence, 2-arylidene-indane-1,3-diones bearing *ortho* substituents on the phenyl ring did not give the corresponding products, even though the reaction was carried out at higher reaction temperature with a prolonged reaction time (entries 10–12, Table 2). The above results showed that the reactivity of substrates significantly depended on both the steric and the electronic effects of the substituents.

The structures of products **5** were fully confirmed by ^{1}H NMR, ^{19}F NMR, IR spectroscopy, mass spectrometry, and elemental analysis. For instance, the characteristic features of ^{1}H NMR in $CDCl_3$ spectra of product **5a** were the appearances of two doublet peaks near $\delta = 4.51$ and 5.19 ppm with $J_{H-H} = 12.5$ Hz for two neighboring protons on cyclohexane moiety, respectively, indicating the *trans* configuration of the vicinal two hydrogen atoms.

Table 1 Optimization of Reaction Conditions for Product **5a**

Entry	Solvent	Base (equiv)	Time (h)	Yield (%)[b]
1	MeCN	–[a]	24	0
2	MeCN	pyridine (0.1)	24	0
3	MeCN	Et_3N (0.1)	24	0
4	MeCN	DBU (0.1)	24	0
5	MeCN	DMAP (0.1)	10	59
6	MeCN	DABCO (0.1)	12	53
7	MeCN	piperidine (0.05)	10	72
8	MeCN	piperidine (0.1)	8	78
9	MeCN	piperidine (0.3)	8	76
10	MeCN	piperidine (0.5)	8	78
11	CH_2Cl_2	piperidine (0.1)	12	70
12	MeOH	piperidine (0.1)	12	44
13	EtOH	piperidine (0.1)	12	47

[a] Without base.
[b] Isolated yields.

Table 2 Scope of the Reaction of Ethyl 4,4,4-trifluoro-3-oxobutanoate **3** and 2-Arylidene-indane-1,3-diones **4**[15–17]

Entry	Ar	Time (h)	Product	Yield (%)[a]
1	Ph	8	**5a**	78
2	4-MeC_6H_4	8	**5b**	75
3	4-$O_2NC_6H_4$	8	**5c**	83
4	4-ClC_6H_4	8	**5d**	81
5	4-FC_6H_4	8	**5e**	80
6	3-ClC_6H_4	8	**5f**	86
7	3-BrC_6H_4	8	**5g**	92
8	4-$MeOC_6H_4$	24	–	–
9	3,4-$(MeO)_2C_6H_3$	24	–	–
10	2-$O_2NC_6H_4$	24	–	–
11	2-ClC_6H_4	24	–	–
12	2,4-$Cl_2C_6H_3$	24	–	–

[a] Isolated yields.

The chemical shift of the CF_3 group in ^{19}F NMR was a singlet peak at δ = –71.65 ppm (s, 3 F), which indicated that the CF_3 group was bonded to a quaternary carbon atom. Furthermore, the structure of product **5a** was confirmed by XRD analysis (Figure 1).[18] The structure revealed that the proton H3 attached to oxygen O3 of hydroxy group formed an intramolecular H bond with the oxygen O1 of carbonyl group of the indan-1,3-dione moiety [distance O1···H3 = 2.233 Å; angle O3–H3···O1 = 132.36°).

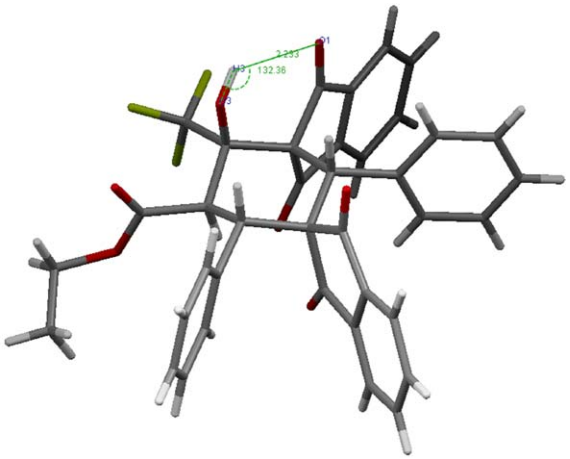

Figure 1 Crystal structure of compound **5a**, showing the intramolecular H bond

A plausible mechanism for this reaction was shown in Scheme 2. Ethyl-4,4,4-trifluoro-1,3-dioxobutanoate reacted with 2-arylidene-indane-1,3-diones to generate the intermediate **A** catalyzed by piperidine via a Michael addition. The intermediate **A** reacted with the second 2-arylidene-indane-1,3-dione to give intermediate **B**, which then underwent an intramolecular cyclization reaction to afford the unexpected highly puckered dispirocyclohexane products **5a**–**g**. This explanation was consistent with the observed results that the reaction for substrates with *ortho* substitution on the phenyl ring was inhibited because of steric hindrance.

In conclusion, we have developed a facile reaction to obtain a series of novel unexpected fluorine-containing multiply substituted dispirocyclohexanes in good yields. This procedure offers several advantages including mild reaction conditions, high yields of products, as well as readily available starting materials, which makes it a useful and attractive process for the construction of fluorinated multiply substituted dispirocyclohexane derivatives.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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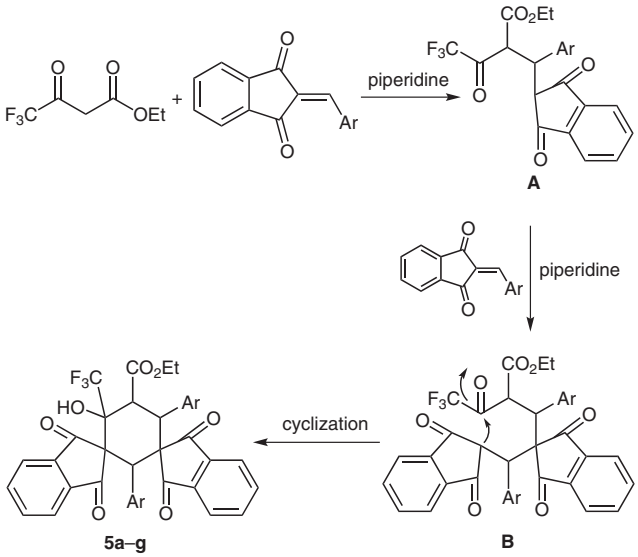

Scheme 2 A plausible mechanism for formation of compounds **5**

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(15) **A Typical Experimental Procedure for the Preparation of 5a**

To a mixture of ethyl 4,4,4-trifluoro-3-oxobutanoate (184.0 mg, 1.0 mmol) and 2-benzylidene-indane-1,3-dione (468.0 mg, 2.0 mmol) in MeCN (3.0 mL) was added a catalytic amount of pipreridine (8.5 mg, 0.1 mmol). The resulting mixture was stirred at r.t. until the reaction was completed (8 h, monitored by TLC). The solvent was removed under reduced pressure. And then the residue was purified by column chromatography on silica gel using PE–EtOAc [6:1 (v/v)] as eluent to afford **5a** as a colorless solid in 78% yield.

(16) **Spectroscopic Data for Products 5**

Compound **5a**: colorless solid (509.0 mg), mp 211–214 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.0 Hz, 3 H, OCH_2CH_3), 3.84 (qd, J_1 = 7.0 Hz, J_2 = 3.5 Hz, 2 H, OCH_2CH_3), 4.51 (d, *J* = 12.5 Hz, 1 H, CH), 4.56 (s, 1 H, CH), 5.19 (d, *J* = 12.5 Hz 1 H, CH), 5.65 (s, 1 H, OH), 6.37 (br, 1 H, ArH), 6.59–7.06 (m, 8 H, ArH), 7.32–7.42 (m, 4 H, ArH), 7.54–7.56 (m, 3 H ArH), 7.66–7.69 (m, 1 H, ArH), 7.93–7.95 (m, 1 H, ArH). ^{19}F NMR (470 MHz, $CDCl_3$): δ = –71.63 (s, 3 F, CF_3). IR (KBr): 3402, 3062, 2981, 2932, 1745, 1711, 1594, 1247, 1184 cm^{-1}. ESI-MS: *m/z* = 653 [M + H]$^+$, 670 [M + NH_4]$^+$. Anal. Calcd for $C_{38}H_{27}F_3O_7$: C, 69.94; H, 4.17. Found: C, 70.06; H, 4.06.

Compound **5b**: colorless solid (510.0 mg), mp 227–229 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.0 Hz, 3 H, OCH_2CH_3), 1.78 (s, 3 H, $ArCH_3$), 2.04 (s, 3 H, $ArCH_3$), 3.84 (qd, J_1 = 7.0 Hz, J_2 = 3.5 Hz, 2 H, OCH_2CH_3), 4.47 (d, *J* = 12.5 Hz, 1 H, CH), 4.51 (s, 1 H, CH), 5.15 (d, *J* = 12.5 Hz, 1 H, CH), 5.63 (s, 1 H, OH), 6.15 (br, 1 H, ArH), 6.50–6.70 (m, 4 H, ArH), 6.82–6.86 (m, 2 H, ArH), 7.24–7.36 (m, 2 H, ArH), 7.39–7.43 (m, 2 H, ArH), 7.66–7.69 (m, 4 H, ArH), 7.92–7.93 (m, 1 H, ArH). ^{19}F NMR (470 MHz, $CDCl_3$): δ = –71.65 (s, 3 F, CF_3). IR (KBr): 3408, 3029, 2986, 1741, 1712, 1247 cm^{-1}. ESI-MS: *m/z* = 681 [M + H]$^+$, 698 [M + NH_4]$^+$. Anal. Calcd for $C_{40}H_{31}F_3O_7$: C, 70.58; H, 4.59. Found: C, 70.33; H, 4.77.

Compound **5c**: colorless solid (617.0 mg), mp 246–247 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.0 Hz, 3 H, OCH_2CH_3), 3.89 (qd, J_1 = 7.0 Hz, J_2 = 3.5 Hz, 2 H, OCH_2CH_3), 4.69 (d, *J* = 12.5 Hz, 1 H, CH), 4.71 (s, 1 H, CH), 5.20 (d, *J* = 12.5 Hz, 1 H, CH), 5.45 (s, 1 H, OH), 6.84–7.28 (m, 4 H, ArH), 7.43–7.53 (m, 3 H, ArH), 7.58–7.71 (m, 5 H, ArH), 7.76–7.80 (m, 2 H, ArH), 7.97–8.00 (m, 2 H, ArH). ^{19}F NMR (470 MHz, $CDCl_3$): δ = –71.67 (s, 3 F, CF_3). IR (KBr): 3420, 3058, 2979, 2934, 1746, 1710, 1595, 1248, 1188 cm^{-1}. ESI-MS: 743 [M + H]$^+$, 760 [M + NH_4]$^+$. HRMS (MALDI/DHB): *m/z* calcd for [$C_{38}H_{25}F_3N_2O_{11}$ + H]$^+$: 743.1483; found: 743.1501; *m/z* calcd for [$C_{38}H_{25}F_3N_2O_{11}$ + Na]$^+$: 765.1303; found:765.1309.

Compound **5d**: colorless solid (584.0 mg), mp 243–244 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.0 Hz, 3 H, OCH_2CH_3), 3.87 (qd, J_1 = 7.0 Hz, J_2 = 3.5 Hz, 2 H, OCH_2CH_3), 4.49 (d, *J* = 12.5 Hz, 1 H, CH), 4.53 (s, 1 H, CH), 5.11 (d, *J* = 12.5 Hz, 1 H, CH), 5.52 (s, 1 H, OH), 6.36–7.07 (m, 7 H, ArH), 7.33–7.51 (m, 4 H, ArH), 7.60–7.72 (m, 3 H, ArH), 7.72–7.75 (m, 1 H, ArH), 7.94–7.96 (m, 1 H, ArH). ^{19}F NMR (470 MHz, $CDCl_3$): δ = –71.70 (s, 3 F, CF_3). IR (KBr): 3408, 3071, 2986, 2937, 1739, 1713, 1593, 1243, 1196 cm^{-1}. ESI-MS: *m/z* = 721, 723, 725 [M + H]$^+$, 738, 740, 742 [M + NH_4]$^+$. Anal. Calcd for $C_{38}H_{25}Cl_2F_3O_7$: C, 63.26; H, 3.49. Found: C, 62.87; H, 3.58.

Compound **5e**: colorless solid (551.0 mg), mp 222–223 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.0 Hz, 3 H, OCH_2CH_3), 3.86 (qd, J_1 = 7.0 Hz, J_2 = 3.5 Hz, 2 H, OCH_2CH_3), 4.49 (d, *J* = 12.5 Hz, 1 H, CH), 4.54 (s, 1 H, CH), 5.11 (d, *J* = 12.5 Hz, 1 H, CH), 5.55 (s, 1 H, OH), 6.09 (br, 1 H, ArH) 6.49–6.93 (m, 6 H, ArH), 7.37–7.49 (m, 4 H, ArH), 7.56–7.60 (m, 3 H, ArH), 7.70–7.73 (m, 1 H, ArH), 7.93–7.95 (m, 1 H, ArH). ^{19}F NMR (470 MHz, $CDCl_3$): δ = –71.71 (s, 3 F, CF_3), –112.61 (m, 1 F, ArF), –114.13 (m, 1 F, ArF). IR (KBr): 3397, 3087, 2983, 2938, 1743, 1711, 1511, 1247, 1190 cm^{-1}. ESI-MS: *m/z* = 689 [M + H]$^+$. Anal. Calcd for $C_{38}H_{25}F_5O_7$: C, 66.28; H, 3.66. Found: C, 66.04; H, 3.49.

Compound **5f**: colorless solid (620.0 mg), mp 241–243 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.94 (br, 3 H, OCH_2CH_3), 3.87 (br, 2 H, OCH_2CH_3), 4.51 (br, 2 H, CH), 5.13 (br, 1 H, CH), 5.58 (s, 1 H, OH), 6.34–7.01 (m, 7 H, ArH), 7.43–8.00 (m, 9 H, ArH). ^{19}F NMR (470 MHz, $CDCl_3$): δ = –71.63 (s, 3 F, CF_3). IR (KBr): 3440, 3055, 2984, 1744, 1710, 1593, 1249, 1235, 1176 cm^{-1}. ESI-MS: *m/z* = 721, 723, 725 $[M + H]^+$, 738, 740, 742 $[M + NH_4]^+$. Anal. Calcd for $C_{38}H_{25}Cl_2F_3O_7$: C, 63.26; H, 3.49. Found: C, 62.91; H, 3.37.
Compound **5g**: colorless solid (743 mg), mp 265–266 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.95 (br, 3 H, OCH_2CH_3), 3.88 (br, 2 H, OCH_2CH_3), 4.48 (br, 2 H, CH), 5.13 (br, 1 H, CH), 5.58 (s, 1 H, OH), 6.61–7.13 (m, 7 H, ArH), 7.35–7.76 (m, 8 H, ArH), 7.95–8.02 (m, 1 H, ArH). ^{19}F NMR (470 MHz, $CDCl_3$): δ = –71.61 (s, 3 F, CF_3). IR (KBr): 3441, 3072, 2983, 1744, 1711, 1592, 1250, 1178 cm^{-1}. ESI-MS: *m/z* = 809, 811, 813 $[M + H]^+$, 826, 828, 830 $[M + NH_4]^+$. HRMS (MALDI/DHB): *m/z* calcd for $[C_{38}H_{25}Br_2F_3O_7 + Na]^+$: 830.9811; found: 830.9817.

(17) In particular, in the cases of compounds **5f** and **5g**, the ^{1}H NMR spectrum showed broad signals due to decreased rotational flexibility of the highly puckered structures.

(18) CCDC 720376 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 (1223)336033.