

3-Oxo-4,4,4-trifluorobutyronitriles as Building Blocks of
Trifluoromethyl Substituted Heterocycles 2. Heterocyclization to 3-
Aryl-4-trifluoromethyl-2*H*-1-benzopyran-2-ones under Hoesch
Reaction Conditions

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Resorcinol and 5-methylresorcinol, respectively, react with 3-oxo-2-aryl-4,4,4-trifluorobutyronitrile using zinc chloride as a catalyst in dibutyl ether under the Hoesch reaction conditions to give a low yield of 3-aryl-7-hydroxy-4-trifluoromethyl- or 3-aryl-5-hydroxy-7-methyl-4-trifluoromethyl-2*H*-1-benzopyran-2-ones. However, the related reaction with *m*-methoxyphenol was found to produce poor yields of 3-aryl-7-methoxy-4-trifluoromethyl-2*H*-1-benzopyran-2-one and its 3,4-dihydro-4-hydroxy derivative.

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Among 2*H*-1-benzopyran-2-one derivatives, some are known as lasing dyes [1] and fluorescent brightening agents [2]. These uses are also found for the 4-trifluoromethyl-substituted derivatives, in particular, those bearing an amino substituent at C-7 [3-7], which may also be useful as a fluorescent marker for the detection of proteinase [8]. They have been synthesized by means of the Pechmann condensation of alkyl 3-oxo-4,4,4-trifluorobutanoate with an appropriate phenol [9,10]. 3-Aryl-4-trifluoromethyl-2*H*-1-benzopyran-2-ones, which appear so far unknown, may find similar uses. During the course of our study on the potentialities of 3-oxo-4,4,4-trifluorobutyronitriles as the building block of trifluoromethyl-substituted heterocycles [11], it occurred to us that the reactions of these ketonitriles bearing an aryl group at C-2 with phenols under Hoesch reaction conditions may provide the target benzopyran-2-ones bearing a 3-aryl group [12]. A literature survey reveals that 3-oxo-2-phenylbutyronitriles [13,14] and benzoylacetone nitrile [15] yield 2*H*-1-benzopyran-2-ones, not the diketones expected from the normal Hoesch reaction, when allowed to react with phenols.

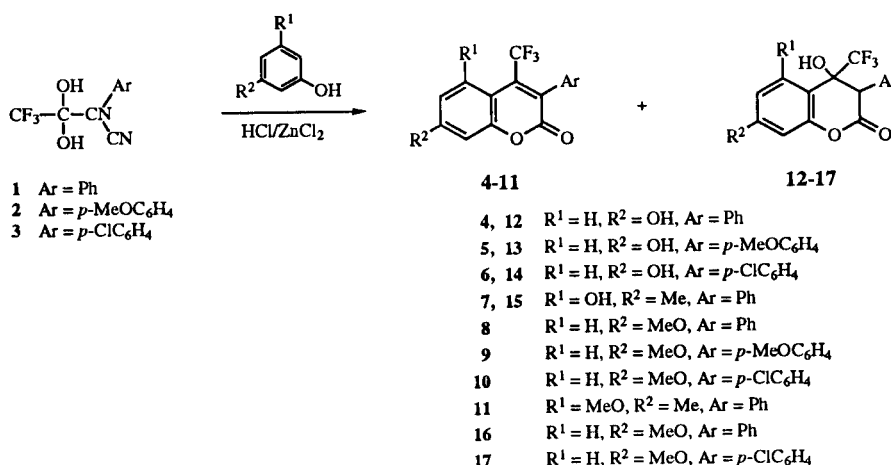
The reaction of 3-oxo-4,4,4-trifluoro-2-phenylbutyronitrile hydrate (**1**) with resorcinol was conducted in the presence of zinc chloride in hot dibutyl ether with hydrogen chloride passing into the reaction mixture. The reaction mixture was extracted with alkali and acidification of the extracts gave the benzopyrone **4** in 17% yield. The reactions of the corresponding 2-(4'-methoxyphenyl)- and 2-(4'-chlorophenyl)butyronitriles **2** and **3**, respectively, with resorcinol were similarly carried out to furnish the benzopyrones **5** (16%) and **6** (30%). The presence of a carbonyl stretching absorption around 1700 cm⁻¹ in their ir spectra eliminates the 7-hydroxy-4*H*-1-benzopyran-4-one structure whose ν (C=O) absorption is usually seen below 1660 cm⁻¹ [16,17]. The ¹H nmr spectra of **4**, **5**, and **6** display a doublet at δ = 6.8 (J = 2 Hz) (8-H), a doublet

doublet at δ = 6.9 (J = 9 and 2 Hz) (6-H), and a finely splitted doublet at δ = 7.6 (J = 9 Hz) (5-H) for the benzopyrone-ring protons.

The appearance of the C-5 proton as a finely split doublet suggests the presence of H-F coupling as reported by Bayer, Pastor, and Cambon [10]. To confirm this point further, compounds **4**, **5**, and **6** were methylated with diazomethane. The ¹H nmr spectra of the 7-methoxy derivatives **8**, **9**, and **10** clearly exhibit a double quartet at δ = 7.7 (J_{H-H} = 9 Hz and ⁵J_{H-F} = 2 Hz).

The reaction of 5-methylresorcinol with **1** produced a compound exhibiting ν (C=O) absorption at 1694 cm⁻¹ in only 6% yield, which was assigned the 5-hydroxy-7-methyl-3-phenyl-4-trifluoromethylbenzopyrone structure **7** rather than the 7-hydroxy-5-methyl derivative, despite the known preference of substitution at C-4 in the Hoesch reaction of 5-methylresorcinol producing ketones [18,19]. This is because the Me-proton resonates 0.25 ppm higher than the C-5-Me of the 5,7-dimethyl-4-trifluoromethylbenzopyrone [10], shows no sign of H-F coupling expected for the Me at C-5 [10], and the ring protons resonate about 0.2 ppm higher than those of **4**, **5**, and **6**. The Me-proton of the methyl ether **11** also lacked H-F coupling. In addition, the uv absorptions at highest wavelength of **7** and **11** showed hypsochromic shift by about 10 nm as compared to that of **4**, **5**, and **6**, and their methyl ethers **8**, **9**, **10**, and the intensity of an absorption at 260 nm also differed.

The corresponding reaction of *m*-methoxyphenol with **1** gave two products. In addition to the expected benzopyrone **9** (5.5% yield), a second product exhibiting ν (C=O) absorption at 1756 cm⁻¹ and being negative to a ferric chloride test was isolated, which was assigned the 4-hydroxy-3,4-dihydrobenzopyrone structure **16** from the following data. The strong ν (C=O) absorption at 1756 cm⁻¹ compares favorably with that of 4-ethyl-4-(4'-pyridyl)-3,4-dihydro-2*H*-1-benzopyran-2-one (ν 1760



cm⁻¹) [20], whereas its ¹H nmr spectrum displays an exchangeable proton (δ = 2.24), a benzylic proton (δ = 4.43), and benzopyrone-ring protons resonating 0.1-0.2 ppm higher than the corresponding protons of **7** and the H-5 proton lacked fine structure. The compound has only an end absorption in the region over 220 nm against a strong absorption (λ 340 nm) of **9**. The reaction of *m*-methoxyphenol with **3** was also studied, from which many intractable sticky materials, together with a negligible yield of **10**, were obtained. Formation of the dihydro compound **17**, though not isolated, was inferred from a singlet at δ = 4.41 in the ¹H nmr spectrum of one oily substance.

The dihydro compounds **12**, **13**, **14**, and **15**, formed by nucleophilic attack of resorcinol on the keto-nitrile carbonyl group followed by cyclization, must be an intermediate of **4**, **5**, **6**, and **7**. The ¹H nmr spectra of materials obtained by silica gel chromatography of the residues after filtering **5** and **6**, respectively, exhibited MeO (δ = 3.69) and benzylic protons (δ = 4.32) associated with the dihydro derivative **13**, and a benzylic proton (δ = 4.42) of **14**, lending support to their formations, though we failed to isolate them by chromatography because their R_f values are close to those of **5** and **6**. Dehydration of **16** to **8** was found to be slow, when heated with *p*-toluenesulfonic acid or in trifluoroacetic acid. This is understandable in the light of its survival under the highly acidic conditions.

Beside the 2*H*-1-benzopyran-2-ones and its 4-hydroxy-3,4-dihydro derivatives, many materials have been formed, but they were mostly intractable oils, defying purification.

EXPERIMENTAL

Melting points were determined in capillary tubes and uncorrected. All solutions were dried over sodium sulfate. The ¹H nmr spectra were obtained on a Hitachi R-250 spectrometer at

250 MHz with tetramethylsilane as the internal standard and the assignments were confirmed by deuterium exchange, where necessary. The spectra were taken in hexadeuteriodimethyl sulfoxide unless otherwise indicated. The *J* values mean the H-H couplings unless otherwise indicated. The ir spectra were determined as nujol mulls and the uv spectra were taken in ethanol. Kiesel gel 60 was used for column chromatography. Zinc chloride of 90% purity was used. All evaporations were carried out in a rotary evaporator. Molar concentration of 3-oxo-4,4,4-trifluoro-2-(4'-methoxyphenyl)butyronitrile (**2**), which is a mixture of the keto and hydrate forms [11], and yields of products derived therefrom are based on the hydrate form.

7-Hydroxy-3-phenyl-4-trifluoromethyl-2*H*-1-benzopyran-2-one (**4**).

A solution of 3-oxo-4,4,4-trifluoro-2-phenylbutyronitrile hydrate (**1**) (4.62 g, 0.02 mole), resorcinol (2.20 g, 0.02 mole), dibutyl ether (80 ml) was added dropwise to a stirred mixture of zinc chloride (6.06 g, 0.044 mole) and dibutyl ether (6 ml) and hydrogen chloride was passed into the mixture maintained at 100-110° for 7 hours. The resulting reddish orange mixture was poured into crushed ice and concentrated hydrochloric acid (40 ml), stirred for 30 minutes at room temperature, and allowed to stand overnight, then extracted with ether. The ethereal solution was washed five times with 50 ml of 2% aqueous sodium hydroxide and the aqueous solution was acidified with dilute hydrochloric acid and extracted with ether. The extracts were dried and evaporated. Trituration of the residue in ether furnished the crude benzopyrone (1.03 g, 17%), recrystallized from methanol as prisms (0.84 g), mp 247-249°; ir: ν 3288 (OH), 1716 and 1694 (C=O) cm⁻¹; uv: λ max 260 sh nm (ϵ 2400), 342 (12500); ¹H nmr: δ 6.85 (d, 1H, *J* = 1.8 Hz, 8-H), 6.93 (dd, 1H, *J* = 9.2 and 2.4 Hz, 6-H), 7.31 (m, 2H, 3-Ar), 7.42 (m, 3H, 3-Ar), 7.64 (d with fine structure, 1H, *J* = 8.6 Hz, ⁵J_{H-F} = about 2 Hz, 5-H), 10.9 (1H, br s, OH).

Anal. Calcd. for C₁₆H₉F₃O₃: C, 62.75; H, 2.96. Found: C, 62.48; H, 2.96.

No attempt was made to detect the 4-hydroxy-3,4-dihydrobenzopyrone **12**.

7-Methoxy-3-phenyl-4-trifluoromethyl-2*H*-1-benzopyran-2-one (**8**).

(a) An ethereal solution of diazomethane was poured into a mixture of the 7-hydroxybenzopyrone (**4**) (0.50 g, 1.6 mmoles) in

ether (30 ml). The mixture was set aside for 5 hours at room temperature, excess of diazomethane was decomposed with acetic acid, and the solution was evaporated. Recrystallization of the residue from methanol gave the methyl ether **8** as rods (0.32 g, 61%), mp 139–140°; ir: ν 1719 (CO) cm^{-1} ; uv: λ max 220 sh nm (ϵ 10500), 260 sh (2200), 340 nm (13500); ^1H nmr (deuteriochloroform): δ 3.91 (s, 3H, MeO), 6.91 (dd, 1H, J = 9.15 and 2.44 Hz, 6-H), 6.96 (d, 1H, J = 2.44 Hz, 8-H), 7.28 (m, 2H, 3-Ar), 7.45 (m, 3H, 3-Ar), 7.74 (dq, 1H, J = 9.15 and $^5J_{\text{H-F}}$ = 1.83 Hz, 5-H).

Anal. Calcd. for $\text{C}_{17}\text{H}_{11}\text{F}_3\text{O}_3$: C, 63.75; H, 3.46. Found: C, 63.90; H, 3.36.

(b) A mixture of *m*-methoxyphenol (3.72 g, 0.03 mole), the ketonitrile **1** (6.93 g, 0.03 mole), and dibutyl ether (70 ml) was added dropwise into a stirred mixture of zinc chloride (9.09 g, 0.066 mole) and dibutyl ether (9 ml) and hydrogen chloride was passed into the mixture as described for **4**. The oily materials were extracted with ether and the extracts were washed with 1% aqueous sodium hydroxide, dried, and evaporated to leave an orange oil. The alkaline washings were acidified, a reddish oil was taken into ether, and the work-up of the extracts left an uncharacterized oil. The above orange oil was chromatographed with hexane, benzene, and chloroform, successively. A sticky material from the hexane-eluate was washed with methanol to give a yet unidentified material (0.08 g), mp 80–83°. A sticky material from the benzene eluate was washed with cold methanol to leave the methyl ether **8** (0.53 g, 5.5%), mp 139–141°, identical (mp, ir, and ^1H nmr) with the product of the method (a). An orange sticky material from the chloroform eluate was heated in hexane (50 ml) for 30 minutes. Recrystallization of the insoluble material from cyclohexane gave the dihydrobenzopyrone **16** as needles (0.52 g), mp 141–143°, negative to a ferric chloride test; ir: ν 3412 br (OH), 1756 ($\text{C}=\text{O}$) cm^{-1} ; uv: λ max end absorption over 220 nm; ^1H nmr (deuteriochloroform): δ 2.24 (s with fine structure, 1H, 4-OH), 3.86 (s, 3H, MeO), 4.43 (s, 1H, 3-H), 6.75 (d, 1H, J = 2.4 Hz, 8-H), 6.80 (dd, 1H, J = 8.6 and 2.4 Hz, 6-H), 7.09 (m, 2H, 3-Ar), 7.30 (m, 3H, 3-Ar), 7.49 (d, 1H, J = 8.6 Hz, 5-H).

Anal. Calcd. for $\text{C}_{17}\text{H}_{13}\text{F}_3\text{O}_4$: C, 60.36; H, 3.87. Found: C, 60.30; H, 3.88.

The ir and ^1H nmr spectra of the hexane soluble material (0.11 g), mp 136–141° after recrystallization from cyclohexane, were almost identical with those of the hexane insoluble material (total yield, 6%).

7-Hydroxy-3-(4'-methoxyphenyl)-4-trifluoromethyl-2H-1-benzopyran-2-one (**5**).

A mixture of resorcinol (1.65 g, 0.015 mole), the ketonitrile **2** (3.92 g, 0.015 mole), and dibutyl ether (60 ml) was added into a stirred mixture of zinc chloride (4.54 g, 0.033 mole) and dibutyl ether (4.5 ml), hydrogen chloride was passed as described for **4**, and the reaction mixture was worked up. Trituration of the resulting orange oil in cold methanol gave the benzopyrone **5** (0.79 g, 16%), recrystallized from aqueous methanol as pale yellow needles (0.39 g), mp 221–223°; ir: ν 3436 (OH), 1714 ($\text{C}=\text{O}$) cm^{-1} ; uv: λ max 220 sh nm (ϵ 24600), 264 sh (3400), 350 (16300); ^1H nmr: δ 3.80 (s, 3H, MeO), 6.84 (d, 1H, J = 2.4 Hz, 8-H), 6.92 (dd, 1H, J = 9.2 and 2.4 Hz, 6-H), 6.98 (dd, 2H, J = 8.5 and 1.8 Hz, 3-Ar), 7.24 (dd, 2H, J = 8.5 and 1.8 Hz, 3-Ar), 7.62 (d with fine structure, 1H, J = 9.2 and $^5J_{\text{H-F}}$ = about 2 Hz, 5-H).

Anal. Calcd. for $\text{C}_{17}\text{H}_{11}\text{F}_3\text{O}_4 \cdot 0.2\text{H}_2\text{O}$: C, 60.07; H, 3.38. Found: C, 60.14; H, 3.43.

Evaporation of the filtrate of **5** and chromatography of the residue with chloroform gave an inseparable [21] 7:3 mixture of the benzopyrone **5** and its dihydro derivative **13** (0.66 g, mp 216–218° after recrystallization from aqueous methanol). Its ^1H nmr spectrum had benzopyrone ring and hydroxy protons of **13** at δ 3.69 (s, 3H, MeO), 4.32 (s, 1H, 3-H), 6.62 (d, 1H, J = 2.4 Hz, 8-H), 6.74 (dd, 1H, J = 9.1 and 2.4 Hz, 6-H), 7.40 (d, 1H, J = 9.1 Hz, 5-H), and 10.3 (s, 1H, OH), in addition to overlapped 3-Ar protons, and protons associated with **5**.

7-Methoxy-3-(4'-methoxyphenyl)-4-trifluoromethyl-2H-1-benzopyran-2-one (**9**).

This compound was prepared from the 7-hydroxybenzopyrone **5** (0.135 g, 0.4 mmole) and ethereal diazomethane. Evaporation of the solvent left the methyl ether **9** (0.11 g, 79%), recrystallized from ethanol as rods (0.05 g), mp 170–171°; ir: ν 1726 ($\text{C}=\text{O}$) cm^{-1} ; uv: λ max 220 nm (ϵ 19500), 343 (17600); ^1H nmr: δ 3.80 (s, 3H, MeO), 3.90 (s, 3H, MeO), 6.99 (d, 2H, J = 8.5 Hz, 3-Ar), 7.07 (d, 1H, J = 9.0 and 2.4 Hz, 6-H), 7.16 (d, 1H, J = 2.4 Hz, 8-H), 7.26 (d, 2H, J = 8.5 Hz, 3-Ar), 7.69 (dq, 1H, J = 9.0 and $^5J_{\text{H-F}}$ = 2.4 Hz, 5-H).

Anal. Calcd. for $\text{C}_{18}\text{H}_{13}\text{F}_3\text{O}_4$: C, 61.72; H, 3.74. Found: C, 61.51; H, 3.87.

3-(4'-Chlorophenyl)-7-hydroxy-4-trifluoromethyl-2H-1-benzopyran-2-one (**6**).

A solution of resorcinol (3.30 g, 0.03 mole), the ketonitrile **3** (7.97 g, 0.03 mole), and dibutyl ether (60 ml) was added into a stirred mixture of zinc chloride (9.09 g, 0.066 mole) and dibutyl ether (9 ml), hydrogen chloride was passed, and work-up of the reaction mixture left a sticky solid. This was washed with cold methanol to give the 7-hydroxybenzopyrone **6** (3.11 g, 30%), recrystallized from aqueous methanol as light yellow rhombic plates (2.89 g), mp 220–222°; ir: ν 3424 (OH), 1698 and 1710 ($\text{C}=\text{O}$) cm^{-1} ; uv: λ max 215 sh nm (ϵ 26300), 262 sh (2700), 345 (20100); ^1H nmr: δ 6.86 (d, 1H, J = 2.4 Hz, 8-H), 6.94 (dd, 1H, J = 8.6 and 2.4 Hz, 6-H), 7.37 (d, 2H, J = 8.6 Hz, 3-Ar), 7.51 (d, 2H, J = 8.6 Hz, 3-Ar), 7.64 (dm, 1H, J = 8.6 Hz, 5-H), 11.0 (br s, 1H, 7-OH).

Anal. Calcd. for $\text{C}_{16}\text{H}_8\text{ClF}_3\text{O}_3$: C, 56.40; H, 2.37. Found: C, 56.55; H, 2.18.

The color faded during the course of drying at 110°/1 mm Hg for 1 hour in an Abderhalden apparatus and this specimen showed a little broadened signals at δ 6.84 (s, 1H, 8-H), 6.92 (d, 1H, J = 7.3 Hz, 6-H), 7.35 (s, 2H, 3-Ar), 7.50 (s, 2H, 3-Ar), 7.62 (s, 1H, 5-H), 11.0 (br s, 1H, OH). The methanolic filtrate of **6** was evaporated and chromatography of the residue with benzene gave a very sticky oil. Elution with chloroform gave an inseparable [21] mixture (0.43 g) of **6** and **14**, whose ^1H nmr showed signals at δ 4.42 (s, 3-H of **14**), 6.74 (d, J = 1.8 Hz, 8-H of **14**), and 7.72 (dm, 5-H of **6**), in addition to overlapped signals at δ 6.76–7.48. The ethereal solution remained after alkaline extractions was chromatographed to give no identifiable materials.

3-(4'-Chlorophenyl)-7-methoxy-4-trifluoromethyl-2H-1-benzopyran-2-one (**10**).

(a) The 7-hydroxybenzopyrone **6** (0.08 g, 0.2 mmole) was treated with ethereal diazomethane. The residue after work-up was chromatographed with benzene to give the methyl ether **10**

(0.04 g, 48%), recrystallized from hexane as rectangular plates, mp 128°; ir: ν 1720 (C=O) cm^{-1} ; uv: λ max 214 nm (ϵ 21100), 260 nm (ϵ 3000), 340 nm (ϵ 19000); ^1H nmr (deuteriochloroform): δ 3.92 (s, 3H, MeO), 6.90 (d, 1H, J = 2.4 Hz, 8-H), 6.96 (dd, 1H, J = 9.2 and 2.4 Hz, 6-H), 7.23 (d, 2H, J = 7.9 Hz, 3-Ar), 7.43 (d, 2H, J = 7.9 Hz, 3-Ar), 7.74 (dq, 1H, J = 9.2 and $^5J_{\text{H-F}}$ = 2.4 Hz).

Anal. Calcd. for $\text{C}_{17}\text{H}_{10}\text{ClF}_3\text{O}_3$: C, 57.56; H, 2.84. Found: C, 57.44; H, 2.81.

(b) A mixture of *m*-methoxyphenol (3.72 g, 0.03 mole), the ketonitrile 3 (7.97 g, 0.03 mole), and dibutyl ether (50 ml) was added into a mixture of zinc chloride (9.09 g, 0.066 mole) and dibutyl ether (9 ml), hydrogen chloride was passed, and the reaction mixture was worked up. Chromatography of a sticky residue with benzene gave 10 (0.17 g, 1.6%), mp 126–127° after recrystallization. Further elution gave a reddish oil (6.81 g) that contained a number of products including 14 (δ 4.41) and the ketonitrile (0.32 g) was recovered by elution with chloroform.

5-Hydroxy-7-methyl-3-phenyl-4-trifluoromethyl-2H-1-benzopyran-2-one (7).

A mixture of 5-methylresorcinol hydrate (4.26 g, 0.03 mole), the ketonitrile 1 (6.93 g, 0.03 mole), and dibutyl ether (70 ml) was added into a mixture of zinc chloride (9.09 g, 0.066 mole) and dibutyl ether (9 ml), and hydrogen chloride was passed. Trituration of an oily residue in cold methanol (2 ml) left a sticky solid, which was stirred in cold methanol (10 ml) for 30 minutes. The solid (0.56 g, 6%) was chromatographed with benzene to give the 5-hydroxybenzopyrone 7, recrystallized from aqueous methanol as yellow needles, mp 238–239°; ir: ν 3308 (OH) and 1694 (C=O) cm^{-1} ; uv: λ max 263 nm (ϵ 6000), 329 nm (ϵ 11100); ^1H nmr (hexadeuterioacetone): δ 2.39 (s, 3H, 7-Me), 2.92 (s, H_2O), 6.77 (s, 2H, 6-H and 8-H), 7.43 (m, 5H, 3-Ar), and 9.74 (br s, 1H, 5-OH).

Anal. Calcd. for $\text{C}_{17}\text{H}_{11}\text{F}_3\text{O}_3\cdot\text{H}_2\text{O}$: C, 60.36; H, 3.87. Found: C, 60.32; H, 3.54.

5-Methoxy-7-methyl-3-phenyl-4-trifluoromethyl-2H-1-benzopyran-2-one (11).

A mixture of the 5-hydroxybenzopyrone 7 (0.16 g, 0.5 mmole) in ether (10 ml) was treated with ethereal diazomethane and chromatography of an oily material with benzene gave the methyl ether 11 (0.08 g, 48%), recrystallized from hexane as pale yellow leaflets (0.04 g), mp 112–114°; ir: ν 1722 (C=O) cm^{-1} ; uv: λ max 260 nm (ϵ 7400), 330 nm (ϵ 14000); ^1H nmr (deuteriochloroform): δ 2.42 (s, 3H, Me), 3.90 (s, 3H, MeO), 6.95 (m,

2H, 6-H and 8-H), 7.33 (m, 2H, 3-Ar), and 7.43 (s, 3H, 3-Ar).

Anal. Calcd. for $\text{C}_{18}\text{H}_{13}\text{F}_3\text{O}_3$: C, 64.67; H, 3.92. Found: C, 64.61; H, 3.89.

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