Journal of Fluorine Chemistry 146 (2013) 80–85

Contents lists available at SciVerse ScienceDirect

Journal of Fluorine Chemistry

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

Reaction of benzyne with fluorinated 1,3-dicarbonyl compounds

Muhammad Zahid [a], Muhammad Farooq Ibad [a], Zharylkasyn A. Abilov [c], Peter Langer [a,b,*]

[a] Institut für Chemie, Universität Rostock, Albert-Einstein-Str. 3a, 18059 Rostock, Germany
[b] Leibniz-Institut für Katalyse e. V. an der Universität Rostock, Albert-Einstein-Str. 29a, 18059 Rostock, Germany
[c] Al-Farabi Kazakh National University, Al-Farabi Ave. 71, 050040 Almaty, Kazakhstan

ARTICLE INFO

Article history:
Received 29 October 2012
Received in revised form 10 December 2012
Accepted 10 December 2012
Available online 19 December 2012

Keywords:
Arenes
Benzyne
Insertions
1,3-Dicarbonyl compounds
Fluorinated compounds

ABSTRACT

The insertion of fluorinated 1,3-dicarbonyl compounds to benzyne resulted in regioselective formation of various fluorinated 1,5-dicarbonyl compounds which are not readily available by other methods. Products include 2-trifluoroacetyl- and 2-(perfluoroalkanoyl)phenylacetic estres, 2-fluoro-2-phenylacetic esters, 1-aryl-2-(2-trifluoroacetylphenyl)ethan-1-ones and other derivatives.

1. Introduction

Organofluorine molecules play an important role as synthetic drugs [1]. 5-Fluorouracil was the first fluorinated drug which was developed as an anti-tumor agent in 1957 [2]. The importance of fluorine containing compounds is based on their metabolic stability and lipophilicity and, thus, high bioavailability. The incorporation of fluoroalkyl groups and particularly the trifluoromethyl (CF_3) group in pharmaceutically and agrochemically relevant molecules have a significant impact on their physical and biological properties [3a]. Fluorinated aceto- and benzophenones, containing a 1,5-dicarbonyl unit connected by a benzene moiety, are of considerable relevance as synthetic intermediates in medicinal chemistry. For example, benzophenone **A**, prepared by a multistep synthetic synthesis starting from 3-(4-fluorophenyl)propanoic acid, was used as a key intermediate during the synthesis of fluorinated pteridines which were reported to act as anti-viral drugs for the treatment of liver diseases (HCV) [3b]. Trifluoroacetophenone **B**, available by a multistep synthesis starting with 3-bromo-5-iodobenzoic acid, was reported to show considerable activity against pain [3c]. Trifluoroacetophenone **C**, which was also prepared in many steps, was reported to exhibit a pronounced antithrombotic activity [3d] (Chart 1).

Herein, we report a new and convenient synthesis of fluorinated aceto- and benzophenones based on the reaction of benzyne with fluorinated 1,3-dicarbonyl compounds. First evidence for the existence of an aryne was reported in 1902 at the University of Rostock: Stoermer and Kahlert observed the formation of 2-ethoxybenzofuran on treatment of 3-bromobenzofuran with bases in ethanol and postulated the formation of *ortho*-didehydrobenzofuran [4a,b]. In 1927, Bachmann and Clarke suspected benzyne as a reactive intermediate of the Wurtz-Fittig synthesis [4b,c]. Wittig, in 1942, suggested the existence of benzyne [4d]. During the last 50 years, the discovery of benzyne had a strong impact in the field of organic chemistry [5]. Despite the indirect evidence for the existence of benzyne, a direct proof was not reported before 2001 [6]. Benzyne as a reagent in synthetic organic chemistry suffered from several drawbacks, such as its high reactivity and the harsh basic conditions required for its generation by the classic protocol [5]. In 1983, Kobayashi described a mild method for the generation of benzyne at moderate temperature which relies on a fluoride-induced 1,2-elimination reaction of *ortho*-(trimethylsilyl)aryltriflates [7]. Recently, Stoltz and coworkers reported the insertion of benzyne into б-bonds of 1,3-dicarbonyl compounds to give (2-acylphenyl)acetates and related products [8]. It was presumed that the reaction proceeds by formal [2+2] cycloaddition and subsequent fragmentation. While benzyne insertions into metal–metal, heteroatom–metal, heteroatom–heteroatom, carbon–metal, and carbon–heteroatom б-bonds had been reported before, the work of Stoltz represented the first mild and direct insertion of benzyne into a carbon–carbon б-bond. Herein, we

* Corresponding author at: Institut für Chemie, Universität Rostock, Albert-Einstein-Str. 3a, 18059 Rostock, Germany.
E-mail address: peter.langer@uni-rostock.de (P. Langer).

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http://dx.doi.org/10.1016/j.jfluchem.2012.12.004

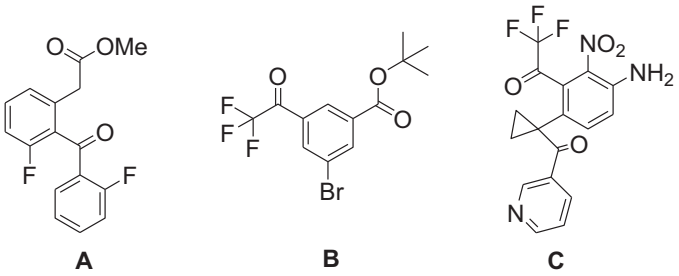
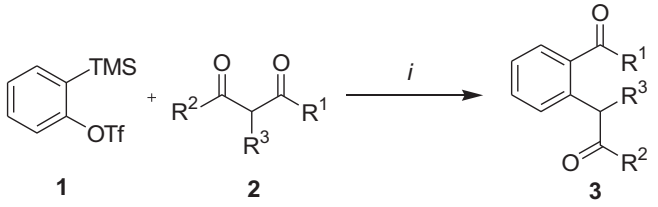


Chart 1. Some important fluorinated 1,5-dicarbonyl compounds.



Scheme 1. Synthesis of **3a–j**. Conditions: i, **1** (0.5 mmol), **2** (0.5 mmol), CsF (1.0 mmol), MeCN (3 mL), 80 °C, 40–60 min.

report what is, to the best of our knowledge, the first application of this method to fluorinated 1,3-dicarbonyl compounds. The transformations reported herein provide an efficient access to fluorinated aceto- and benzophenones which contain a 1,5-dicarbonyl unit connected by a benzene moiety. The products are not readily available by other methods.

2. Results and discussion

The CsF mediated reaction of ethyl 2-fluoroacetoacetate (**2a**) with *ortho*-(trimethylsilyl)aryltriflate **1**, following the conditions reported by Stoltz, afforded the fluorinated product **3a** in 71% yield (Scheme 1, Table 1). This result shows that the reaction is compatible with the presence of a fluorine atom present at carbon atom C-2 of the β-ketoester. The reaction of ethyl 4,4,4-trifluoroacetoacetate (**2b**) with **1** gave fluorinated product **3b** in again 71% yield. This result shows that electron poor, CF_3-substituted β-ketoesters can be successfully employed to give trifluoroacetyl-substituted products. Starting with β-ketoesters **2c**,**d**, containing a fluorinated phenyl group, products **3c**,**d** were prepared. For comparison, we also studied the employment of β-ketoester **2e** which contains a (strong electron-withdrawing) nitro substituent. Its reactions with **1** gave product **3e** in 85% yield. The synthesis of **3c–e** shows that β-ketoesters containing electron withdrawing aryl groups can be successfully used. This methodology was successfully extended to fluorinated 1,3-diketones producing high yields of the corresponding regioselective products (Table 1). It was observed that fluorinated, trifluoromethyl- and perfluoroalkyl-substituted ketoesters and diketones gave the desired acyl-alkylation products in good yields. The coupling of aryne precursor **1** with fluorinated β-diketones **2f–j** was also examined. These β-diketones reacted with **1** to produce side-chain fluorinated *ortho*-disubstituted arenes **3f–j** in good yields.

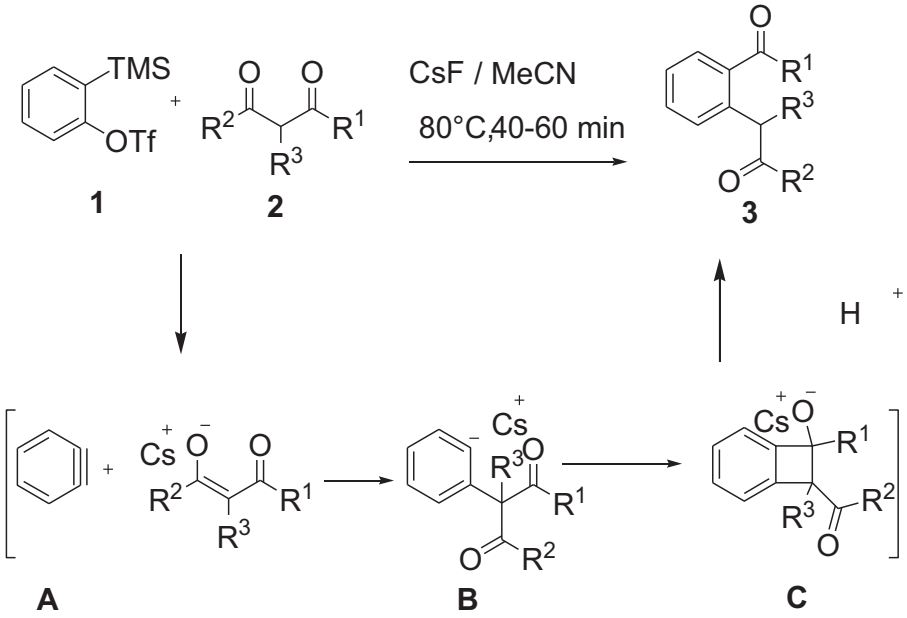
Table 1
Synthesis of **3a–j**.

2,3	R^1	R^2	R^3	Yield (%)[a]
a	Me	EtO	F	71
b	CF_3	EtO	H	71
c	4-FC_6H_4	MeO	H	87
d	4-FC_6H_4	EtO	H	79
e	4-$(NO_2)C_6H_4$	EtO	H	85
f	C_3F_7	t-Bu	H	50
g	CF_3	Ph	H	73
h	CF_3	2-Naphthyl	H	57
i	CF_3	Me	H	67
j	CF_3	2-Furyl	H	70

[a] Yields of isolated products.

The formation of the products can be explained by the mechanism suggested by Stoltz and coworkers [8]: The insertion of benzyne into the α,β (C–C) single bond of the β-ketoesters and β-diketones presumably proceeds by a domino [2+2] cycloaddition/fragmentation reaction via intermediates **A**, **B**, and **C** (Scheme 2). Related domino reactions were reported by other authors [9,10].

The structures of the products were independently verified by 2D-NMR experiments (COSY, HMBC, NOESY). Two regioisomers have to be taken into account, namely, isomers **D** and **E** in case of



Scheme 2. Mechanism proposed by Stoltz et al. [8] for the acyl-alkylation of benzyne.

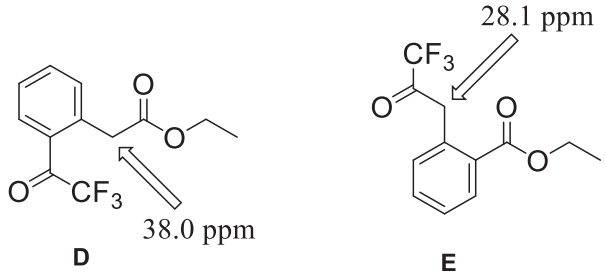


Fig. 1. Possible regiomers of **3b**.

3b (Fig. 1). For the CH_2 group, no splitting (due to fluorine coupling) was observed in the ^{13}C NMR spectrum which suggests that isomer **D** is present. This structure was also supported by mass fragmentation pattern. The base peak $m/z = 187$ gave some evidence for a trifluoroacetyl group directly bonded to the benzene moiety. This base peak is generated by sequential loss of an ethyl group and CO_2. In case of isomer **E**, two fragments should be observed, i.e. one 1,1,1-trifluoropronoyl with $m/z = 111$ and a second ethyl benzoate with $m/z = 150$. Both of these fragments were found to be absent.

In the ^{13}C NMR of 1,3-diketone **3g**, again no long rang splitting of the CH_2 group was observed. Furthermore, the GC–MS fragmentation pattern was in favor of isomer **F** (Fig. 2). The structure was independently confirmed by 2D-NMR (Fig. 3). The carbonyl group resonating at $\delta = 198.3$ ppm showed a clear HMBC interaction with the CH_2 protons. In addition, an HMBC coupling was also observed between an aromatic proton resonating at $\delta = 7.72$ ppm and the carbon of the trifluoroacetyl group which confirmed the direct bonding of the latter to the aromatic ring (isomer **F**). The position of each proton and carbon was located by NOESY, COSY and ^1H NMR. The ^{19}F coupling of the carbon signals in the ^{13}C NMR spectrum further supported structure **F**.

The structure of **3e** was also confirmed by 2D NMR experiments. A clear HMBC correlation of the carbonyl carbon ($\delta = 196.2$ ppm) with two protons ($\delta = 7.89$ ppm) of the benzene ring, containing the nitro group, and with one aromatic proton ($\delta = 7.46$ ppm) of the second benzene ring were observed. The ester carbonyl carbon showed a clear correlation with the protons of both CH_2 groups ($\delta = 3.88, 3.95$ ppm). To locate the exact position of the correlating protons, COSY and NOESY measurements were carried out (Fig. 4).

In conclusion, we have reported the reaction of fluorinated 1,3-dicarbonyl compounds with benzyne. These reactions resulted in the regioselective formation of various fluorinated acetophenones and benzophenones containing a 1,5-dicarbonyl moiety connected by a benzene ring. The products, such as 2-trifluoroacetyl- and 2-(perfluoroalkanoyl)phenylacetic esters, 2-fluoro-2-phenylacetic esters, or 1-aryl-2-(2-trifluoroacetylphenyl)ethan-1-ones, are of pharmacological relevance and not readily available by other methods.

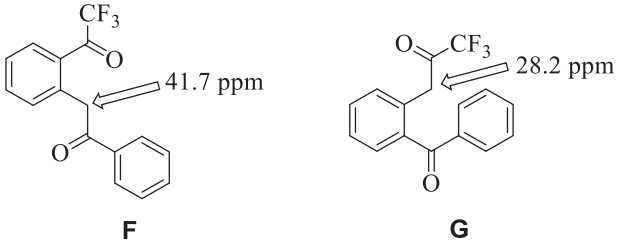


Fig. 2. Possible regiomers of **3g**.

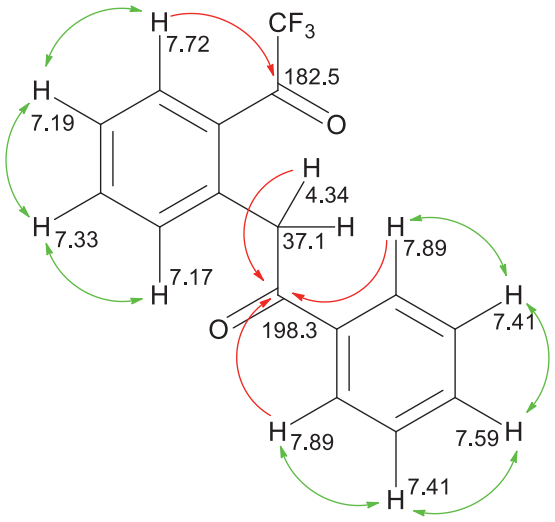


Fig. 3. HMBC, and NOESY interpretation of **3g** (HMBC: single headed, COSY: double headed).

3. Experimental

3.1. General remarks

Reactions were carried out under inert atmosphere (Argon). Solvents for reactions were dried and distilled by standard methods or purchased from Merck®, Aldrich®, Acros Organics®, and others whenever exclusion of water was desired. Solvents for liquid chromatography and extraction were always distilled prior to use and partly reused after fractional distillation (*n*-heptane, ethyl acetate). Bruker AC 250, Bruker ARX 300, Bruker ARX 500. For NMR characterization the one-dimensional ^1H NMR, proton-decoupled ^{13}C NMR, and DEPT 135 spectra were collected. If necessary other techniques (NOESY, COSY, HMQC, and HMBC) were applied as well. All NMR spectra presented in this work, were collected in DMSO-d_6 and $CDCl_3$ solution. All chemical shifts were given in ppm. References (^1H NMR): TMS ($\delta = 0.00$) or residual $CHCl_3$ ($\delta = 7.26$) were taken as internal standard. References (^{13}C NMR): TMS ($\delta = 0.0$) or residual $CHCl_3$ ($\delta = 77.0$) were taken as internal standard. Multiplicities are given as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal. More complex coupling patterns are represented by combinations of the respective symbols. For example, td indicates a triplet of

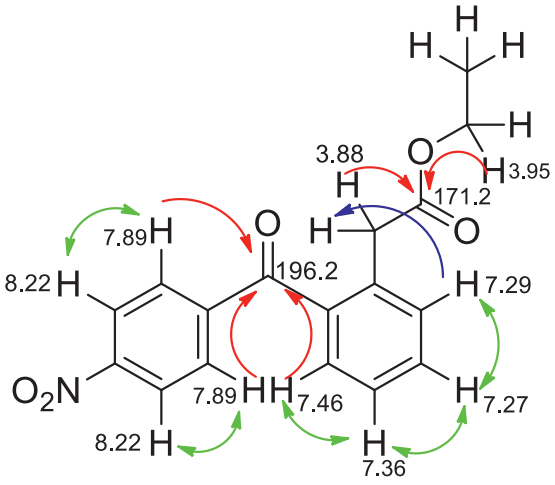


Fig. 4. HMBC, NOESY and COSY interpretation of **3e** (HMBC: single headed, COSY: double headed; NOESY: single headed arrow beginning at the proton with $\delta = 7.29$).

doublets with the larger coupling constant associated with the first symbol (here: triplet). Infrared Spectroscopy (IR): Nicolet 205 FT-IR, Nicolet Protége 460 FT-IR Peaks are given the following assignments: w = weak, m = medium, s = strong, br = broad. Mass Spectrometry (MS): AMD MS40, Varian MAT CH 7, MAT 731 (EI, 70 eV), Intecta AMD 402 (EI, 70 eV and CI), Finnigan MAT 95 (CI, 200 eV). High Resolution Mass Spectrometry (HRMS): Varian MAT 311, Intecta AMD 402. Elemental Analysis: LECO CHNS-932 Thermoquest Flash EA 1112. Melting Points: Micro heating table HMK 67/1825 Kuestner (Büchi Apparatus). Leitz Labolux 12 Pol with heating table Mettler FP 90. Melting points are uncorrected. Thin Layer Chromatography (TLC): Merck Silica gel 60 F254 on aluminum foil from Macherey-Nagel. Detection was carried out under UV light at 254 nm and 365 nm. As colorizing reagent the following mixtures were used: 1–2/100 p-Anisaldehyde or vanillin, 10/100 glacial acetic acid, 5/100 sulfuric acid, 83–84/100 methanol. Column chromatography: column chromatography was performed with Merck Silica Gel 60 or Macherey-Nagel Silica Gel 60 (0.063–0.200 mm, 70–230 mesh). The finer Merck Silica Gel 60 (0.040–0.063 mm, 230–400 mesh) was chosen when appropriate.

3.2. General procedure for the synthesis of compounds **3a–j**

A flame dried 100 mL round bottom flask equipped with magnetic stir bar was charged with acetonitrile (3 mL). The β-ketoester/β-diketone (0.4 mmol, 1.0 equiv.), 2-(trimethylsilyl)-phenyl trifluoromethanesulfonate (**1**) (0.5 mmol, 1.25 equiv.), and cesium fluoride (1.0 mmol, 2.5 equiv.) were sequentially added to the flask. A septum was placed on the reaction vessel, and the mixture was then heated at 80 °C for 45–60 min. When the benzyne precursor was consumed by TLC analysis, the mixture was extracted with brine (4 mL). The aqueous layer was back-extracted with DCM (3× 4 mL). The organic layers were combined and dried over Na_2SO_4. After filtration, the residue was concentrated under reduced pressure and purified by flash chromatography.

3.3. Ethyl 2-(2-acetylphenyl)-2-fluoroacetate (**3a**)

Starting with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**1**) (186 mg, 0.63 mmol), ethyl 2-fluoro-3-oxobutanoate (**2a**) (74 mg, 0.5 mmol), CsF (190 mg, 1.25 mmol) in MeCN (3 mL), was heated up to 80 °C under argon for 45 min, **3a** was isolated after column chromatography (silica gel, 2% EtOAc in *n*-heptane) as a colorless oil (80 mg, 71%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (t, J = 7.4 Hz, 3H, CH_3), 2.54 (s, 3H, CH_3), 4.15 (q, J = 7.7 Hz, 2H, CH_2), 6.51 (d, J = 45.3 Hz, 1H, CH-F), 7.42 (t, J = 7.4 Hz, 1H, Ar), 7.53 (t, J = 7.4 Hz, 1H, Ar), 7.73 (d, J = 8.2 Hz, Ar), 7.77 (d, J = 8.2 Hz, 1H, Ar); ^{19}F NMR (63 MHz, $CDCl_3$): δ = −185.6 (s, 1F, CH-F); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 28.5 (CH_3), 61.8 (CH_2), 87.9 (d, J_{CF} = 177.2 Hz, CH), 126.9 (d, J_{CF} = 14.3 Hz, CH, Ar), 128.8 (d, J_{CF} = 1.7 Hz, CH, Ar), 129.8 (CH), 132.6 (d, J_{CF} = 1.4 Hz, CH, Ar), 135.1 (d, J_{CF} = 18.7 Hz, C, Ar), 136.6 (d, J_{CF} = 2.8 Hz, C, Ar), 168.1 (d, J_{CF} = 25.5 Hz, CO), 200.7 (CO); IR (ATR): $\tilde{\nu}$ = 2979 (w), 1731 (s), 1599, 1368 (w), 1212, 1023 (s), 888 (m), 759, 695 (s) cm^{-1}; GC–MS (EI, 70 eV): m/z (%) = 224 (5, [M]$^+$), 195 (11), 177 (29), 149 (100), 105 (13), 77 (10); HRMS (EI): calcd. For $C_{12}H_{13}O_3F$ [M]$^+$: 224.0849. Found: 224.0850.

3.4. Ethyl 2-(2-(2,2,2-trifluoroacetyl)phenyl)acetate (**3b**)

Starting with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**1**) (186 mg, 0.63 mmol), ethyl 4,4,4-trifluoro-3-oxobutanoate (**2b**) (92 mg, 0.5 mmol), CsF (190 mg, 1.25 mmol) in MeCN (3 mL), was heated up to 80 °C under argon for 45 min, **3b** was isolated after column chromatography (silica gel, 2% EtOAc in *n*-heptane) as a colorless oil (92 mg, 71%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18 (t, J = 7.15 Hz, 3H, CH_3), 3.90 (s, 2H, CH_2), 4.08 (q, J = 7.15 Hz, 2H, CH_2), 7.28 (dd, J = 7.6, 0.8 Hz, 1H, Ar), 7.38 (dt, J = 7.7, 1.2 Hz, 1H, Ar), 7.53 (dt, J = 7.6, 1.3 Hz, 1H, Ar), 7.88 (dd, J = 7.8, 1.6 Hz, 1H, Ar); ^{19}F NMR (63 MHz, $CDCl_3$): δ = −71.3 (s, 3F, CF_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 40.1, 61.1 (CH_2), 116.3 (q, J_{CF} = 292.3 Hz, CF_3), 127.6 (CH), 129.9 (C), 130.4 (q, J_{CF} = 3.8 Hz, CH, Ar), 133.1 (CH), 134.2 (CH), 137.2 (C), 170.6 (CO), 182.5 (q, J_{CF} = 34.7 Hz, CO); IR (ATR): $\tilde{\nu}$ = 3218 (w), 1740 (m), 1465, 1405, 1268 (w), 1170 (s), 1097, 1030, 895 (m), 870, 846 (w), 773, 736, 712 (s), 612, 544 (m) cm^{-1}; GC–MS (EI, 70 eV): m/z (%) = 260 (10, [M]$^+$), 215 (26), 214 (28), 191 (57), 187 (100), 137 (47), 135 (56), 119 (60), 90 (37), 89 (40); HRMS (EI): calcd. For $C_{18}H_{11}O_3F_3$ [M]$^+$: 260.0659. Found: 260.0655.

3.5. Methyl 2-(2-(4-fluorobenzoyl)phenyl)acetate (**3c**)

Starting with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**1**) (186 mg, 0.63 mmol), methyl 3-(4-fluorophenyl)-3-oxopropanoate (**2c**) (98 mg, 0.5 mmol), CsF (190 mg, 1.25 mmol) in MeCN (3 mL), was heated up to 80 °C under argon for 45 min, **3c** was isolated after column chromatography (silica gel, 2% EtOAc in *n*-heptane) as a colorless oil (118 mg, 87%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.45 (s, 3H, CH_3), 3.7 (s, 2H, CH_2), 7.02 (t, J = 9.2 Hz, 2H, Ar), 7.23–7.26 (m, 3H, Ar), 7.34–7.39 (m, 1H, Ar), 7.73 (dd, J = 5.4, 5.2 Hz, 2H, Ar); ^{19}F NMR (63 MHz, $CDCl_3$): δ = -105.3 (s, F); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.5 (CH_2), 51.3 (CH_3), 114.4 (d, J_{CF} = 22.1 Hz, CH, Ar), 125.4 (C), 125.6 (CH), 127.6 (C), 128.7, 129.9, 130.8 (CH), 132.1 (d, J_{CF} = 9.4 Hz, CH, Ar), 132.8 (C), 133.1 (d, J_{CF} = 2.9 Hz, CH, Ar), 137.1, 164.6 (d, J_{CF} = 250.3 Hz, C, Ar), 170.7, 190.5 (CO); IR (ATR): $\tilde{\nu}$ = 2997 (w), 1732, 1656, 1595 (s), 1503, 1434, 1408 (w), 1267, 1223, 1147 (s), 1095, 1010, 941 (w), 918, 851 (m), 808, 783 (w), 741 (s), 632 (w), 600 (s) cm^{-1}; GC–MS (EI, 70 eV): m/z (%) = 272 (6, [M]$^+$), 213 (36), 212 (100), 183 (28), 123 (12), 95 (13); HRMS (EI): calcd. For $C_{16}H_{13}FO_3$ [M]$^+$: 272.0843. Found: 272.0839.

3.6. Ethyl 2-(2-(4-fluorobenzoyl)phenyl)acetate (**3d**)

Starting with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**1**) (186 mg, 0.63 mmol), ethyl 3-(4-fluorophenyl)-3-oxopropanoate (**2d**) (105 mg, 0.5 mmol), CsF (190 mg, 1.25 mmol) in MeCN (3 mL), was heated up to 80 °C under argon for 60 min, **3d** was isolated after column chromatography (silica gel, 2% EtOAc in *n*-heptane) as a colorless oil (113 mg, 79%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.03 (t, J = 7.8 Hz, 3H, CH_3), 4.79 (s, 2H, CH_2), 4.94 (q, J = 7.1 Hz, 2H, CH_2), 8.04 (t, J = 10.1 Hz, 2H, CH, Ar), 8.24–8.29 (m, 3H, Ar), 8.36–8.42 (m, 1H, Ar), 8.76 (dd, J = 6.3, 3.9 Hz, 2CH, Ar); ^{19}F NMR (63 MHz, $CDCl_3$): δ = −105.3 (s, F); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 38.7, 60.8 (CH_2), 115.4 (d, J_{CF} = 21.5 Hz, CH, Ar), 126.5, 129.7, 130.9, 131.8 (CH), 133.0 (d, J_{CF} = 8.6 Hz, CH, Ar), 134.0 (C), 134.1 (d, J_{CF} = 4.5 Hz, C, Ar), 138.5 (C), 165.7 (d, J_{CF} = 248.6 Hz, C, Ar), 171.3, 198.5 (CO); IR (ATR): $\tilde{\nu}$ = 2980 (w), 1730, 1656, 1595 (s), 1503 (m), 1446, 1408, 1368, 1333 (w), 1267, 1147 (s), 1094, 1026, 918, 850 (m), 783 (w), 741 (w), 688 (m), 601 (s) cm^{-1}; GC-MS (EI, 70 eV): m/z (%) = 286 (3, [M]$^+$), 257 (19), 241 (15), 213 (47), 212 (100), 183 (30), 165 (12); HRMS (EI): calcd. For $C_{17}H_{15}FO_3$ [M]$^+$: 286.0999; Found: 286.0992.

3.7. Ethyl 2-(2-(4-nitrobenzoyl)phenyl)acetate (**3e**)

Starting with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**1**) (186 mg, 0.63 mmol), ethyl 3-(4-nitrophenyl)-3-oxopropanoate (**2e**) (119 mg, 0.5 mmol), CsF (190 mg, 1.25 mmol) in MeCN (3 mL), was heated up to 80 °C under argon for 60 min, **3e** was isolated after column chromatography (silica gel, 2% EtOAc in *n*-heptane) as a colorless oil (133 mg, 85%). ^{1}H NMR (300 MHz,

$CDCl_3$): δ = 1.07 (t, J = 6.9 Hz, 3H, CH_3), 3.88 (s, 2H, CH_2), 3.95 (q, J = 5.9 Hz, 2H, CH_2), 7.26–7.38 (m, 3H, Ar), 7.41–7.46 (m, 1H, Ar), 7.89 (d, J = 8.8 Hz, 2H, Ar), 8.22 (d, J = 9.8 Hz, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 38.7, 60.9 (CH_2), 123.4, 126.7 (CH), 129.1, 129.5 (C), 130.1, 131.1, 131.7, 132.1, 134.5, 137.1 (CH), 142.8, 150.0 (C), 171.2, 196.2 (CO); IR (ATR): $\tilde{\nu}$ = 2980 (w), 1727, 1667 (s), 1601 (w), 1521 (s), 1445, 1406 (w), 1343, 1263, 1213, 1153 (s), 1025, 920, 866 (m), 850 (s), 821, 789 (w), 759 (m), 710 (s), 652 (m) cm^{-1}; GC–MS (EI, 70 eV): m/z (%) = 313 (7, $[M]^+$), 296 (36), 268 (21), 267 (16), 240 (33), 239 (100), 194 (41), 165 (64); HRMS (EI): calcd. For $C_{17}H_{15}NO_5$ $[M]^+$: 313.0945; Found: 313.0941.

3.8. 3,3,4,4,5,5,5-Heptafluoro-1-(2-pivaloylphenyl)pentan-2-one (**3f**)

Starting with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**1**) (186 mg, 0.63 mmol), 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyloctane-3,5-dione (**2f**) (74 mg, 0.5 mmol), CsF (148 mg, 1.25 mmol) in MeCN (3 mL), was heated up to 80 °C under argon for 50 min, **3f** was isolated after column chromatography (silica gel, 1% EtOAc in *n*-heptane) as a colorless oil (93 mg, 50%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (s, 9H, $3CH_3$), 3.42 (s, 2H, CH_2), 7.30 (d, J = 7.6 Hz, 1H, Ar), 7.36 (t, J = 8.6 Hz, 1H, Ar), 7.59 (t, J = 7.6 Hz, 1H, Ar), 8.17 (d, J = 8.6 Hz, 1H, Ar); ^{19}F NMR (63 MHz, $CDCl_3$): δ = −124.9 (m, CF_2), −80.5 (m, CF_2), −71.4 (CF_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.9 ($3CH_3$), 35.6 (CH_2), 66.1 (C), 99.7–101.2 (m, CF_2), 105.8–106.2 (m, CF_2), 119.1–120.3 (m, CF_3), 125.5, 127.6, 129.3, 134.6 (CH), 136.8, 137.7 (C), 162.9, 196.3 (CO); IR (ATR): $\tilde{\nu}$ = 3233, 3065, 2228, 1591 (w), 1489, 1329 (m), 1165 (w), 1068, 929 (m), 857 (w), 779 (m), 747 (s) cm^{-1}; GC–MS (EI, 70 eV): m/z (%) = 372 (6, $[M]^+$), 202 (64), 188 (12), 187 (100), 169 (13), 160 (47), 145 (32), 131 (18), 89 (43); HRMS (EI): calcd. For $C_{16}H_{15}F_7O_2$ $[M]^+$: 372.0960; Found: 372.0968.

3.9. 3-(2-Benzoylphenyl)-1,1,1-trifluoropropan-2-one (**3g**)

Starting with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**1**) (186 mg, 0.63 mmol), 4,4,4-trifluoro-1-phenylbutane-1,3-dione (**2g**) (108 mg, 0.5 mmol), CsF (148 mg, 1.25 mmol) in MeCN (3 mL), was heated up to 80 °C under argon for 45 min, **3g** was isolated after column chromatography (silica gel, 2% EtOAc in *n*-heptane) as a colorless oil (107 mg, 73%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.34 (s, 2H, CH_2), 7.21–7.34 (m, 3H, Ar), 7.36–7.49 (m, 2H, Ar), 7.59 (d, J = 7.6 Hz, 1H, Ar), 7.72 (t, J = 7.6 Hz, 2H, Ar), 7.89 (d, J = 7.6 Hz, 1H, Ar); ^{19}F NMR (63 MHz, $CDCl_3$): δ = −71.4 (s, 3F, CF_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.1 (CH_2), 112.4 (C), 116.3 (q, J_{CF} = 292 Hz, C), 126.4, 128.3, 129.1 (CH), 129.7 (C), 130.2, 130.3, 130.5, 132.9, 133.1, 133.9 (CH), 136.7, 138.4 (C), 182.5 (q, J_{CF} = 34.7 Hz, CO), 198.3 (CO); IR (ATR): $\tilde{\nu}$ = 3062 (w), 1715 (m), 1659 (s), 1596 (m), 1571, 1485 (w), 1447, 1269 (m), 1180, 1138 (s), 1000 (w), 935, 733, 698, 664, 639 (s) cm^{-1}; GC–MS (EI, 70 eV): m/z (%) = 292 (48, $[M]^+$), 195 (21), 187 (100), 165 (32), 105 (51), 77 (43), 75 (10); HRMS (EI): calcd. For $C_{16}H_{11}F_3O_2$ $[M]^+$: 292.0711. Found: 292.0708.

3.10. 2,2,2-Trifluoro-1-(2-(2-(naphth-2-yl)-2-oxoethyl)phenyl)ethanone (**3h**)

Starting with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**1**) (186 mg, 0.63 mmol), 4,4,4-trifluoro-1-(naphthalen-2-yl)butane-1,3-dione (**2h**) (133 mg, 0.5 mmol), CsF (148 mg, 1.25 mmol) in MeCN (3 mL), was heated up to 80 °C under argon for 50 min, **3h** was isolated after column chromatography (silica gel, 2% EtOAc in *n*-heptane) as a colorless oil (97 mg, 57%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.14 (s, 2H, CH_2), 7.37 (dd, J = 7.6, 7.2 Hz, 1H, Ar), 7.49–7.52 (m, 2H, Ar), 7.70–7.88 (m, 4H, Ar), 8.04 (d, J = 7.6 Hz, 1H, Ar), 8.08 (d, J = 7.6 Hz, 1H, Ar), 8.16 (d, J = 8.6 Hz, 1H, Ar), 8.42 (s, 1H, Ar); ^{19}F NMR (63 MHz, $CDCl_3$): δ = −71.3 (s, 3F, CF_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.2 (CH_2), 117.3 (q, J_{CF} = 280 Hz, CF_3), 120.9 (C), 124.4, 126.7, 126.9, 127.9, 128.3, 128.6, 128.9, 129.1, 129.4, 129.9 (CH), 132.5, 132.7, 134.6 (C), 135.9 (CH), 138.5 (C), 180.6 (q, J_{CF} = 33.5 Hz, CO), 198.2 (CO); IR (ATR): $\tilde{\nu}$ = 3058 (w), 1714 (m), 1654 (s), 1625, 1596 (m), 1571 1486, 1464, 1446, 1352 (w), 1291, 1275 (m), 1181, 1138 (s), 982 (w), 937 (s), 865, 825 (w), 784 (m), 750, 732, 663 (s), 602 (m), 574 (w) cm^{-1}; GC-MS (EI, 70 eV): m/z (%) = 342 (7, $[M]^+$), 258 (100), 245 (34), 228 (24), 155 (45), 127 (100), 114 (34), 105 (37), 75 (9); HRMS (EI): calcd. For $C_{20}H_{13}F_3O_2$ $[M]^+$: 342.0868; Found: 342.0869.

3.11. 1-(2-(2,2,2-Trifluoroacetyl)phenyl)propan-2-one (**3i**)

Starting with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**1**) (186 mg, 0.63 mmol), 1,1,1-trifluoropentane-2,4-dione (**2i**) (77 mg, 0.5 mmol), CsF (103 mg, 1.25 mmol) in MeCN (3 mL), was heated up to 80 °C under argon for 60 min, **3i** was isolated after column chromatography (silica gel, 2% EtOAc in *n*-heptane) as a colorless oil (77 mg, 67%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.09 (s, 3H, CH_3), 4.19 (s, 2H, CH_2), 6.26 (d, J = 7.5 Hz, 1H, Ar), 6.37 (t, J = 6.4 Hz,1H, Ar), 6.59 (t, J = 6.4 Hz,1H, Ar), 7.17 (d, J = 7.4 Hz, 1H, Ar); ^{19}F NMR (63 MHz, $CDCl_3$): δ = −70.8 (s, 3F, CF_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.7 (CH_3), 45.6 (CH_2), 116.6 (q, J_{CF} = 274.7 Hz, CF_3), 120.6 (C), 124.8, 127.5, 129.5, 134.7 (CH), 136.5 (C), 173.6 (q, J_{CF} = 34.5 Hz, CO), 193.1 (CO); IR (ATR): $\tilde{\nu}$ = 2953 (w), 1585, 1402 (m), 1278, 1069 (s), 973 (m), 900, 796, 735, 694, 672 (s), 639, 555 (m) cm^{-1}; GC–MS (EI, 70 eV): m/z (%) = 230 (10, $[M]^+$), 179 (32), 185 (14), 173 (41), 151 (100), 152 (10), 77 (51), 75 (14); HRMS (EI): calcd. For $C_{11}H_9F_3O_2$ $[M]^+$: 230.0555; Found: 230.0557.

3.12. 2,2,2-Trifluoro-1-(2-(2-(furan-2-yl)-2-oxoethyl)phenyl)ethanone (**3j**)

Starting with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**1**) (186 mg, 0.63 mmol), 4,4,4-trifluoro-1-(furan-2-yl)butane-1,3-dione (**2j**) (119 mg, 0.5 mmol), CsF (103 mg, 1.25 mmol) in MeCN (3 mL), was heated up to 80 °C under argon for 50 min., **3j** was isolated after column chromatography (silica gel, 2% EtOAc in *n*-heptane) as a colorless oil (99 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.42 (s, 2H, CH_2), 6.71 (d, J = 5.9 Hz, 2H, Ar), 6.85 (t, J = 6.8 Hz, 1H, Ar), 7.42–7.46 (m, 2H, Ar), 7.81 (d, J = 8.8 Hz, 1H, Ar), 8.22 (d, J = 8.8 Hz, 1H, Ar); ^{19}F NMR (63 MHz, $CDCl_3$): δ = −69.8 (s, 3F, CF_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 43.7 (CH_2), 112.6 (CH), 114.6 (q, J_{CF} = 274.7 Hz, CF_3), 118.4, 127.1, 127.5, 127.9, 128.5, 128.9 (CH), 129.8 (C), 147.5 (CH), 151.4 (C), 184.2 (q, J_{CF} = 34.5 Hz, CO), 207.6 (CO); IR (ATR): $\tilde{\nu}$ = 3150 (w), 1731 (s), 1642 (m), 1478 (s), 1549 (m), 1445 (m), 1228 (m), 1162 (m), 1003 (m), 815 (m), 746 (s) cm^{-1}; GC–MS (EI, 70 eV): m/z (%) = 282 (2, $[M]^+$), 213 (14), 212 (100), 184 (79), 128 (73), 89 (17); HRMS (EI): calcd. For $C_{14}H_9F_3O_3$ $[M]^+$: 282.0504. Found: 282.0506.

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