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Nucleophilic trifluoromethylation of anhydrides employing (trifluoromethyl)trimethylsilane: Synthesis of γ-trifluoromethylated γ-butyrolactones

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ABSTRACT

Fluoride-catalyzed nucleophilic trifluoromethylation of acid anhydrides using CF_3SiMe_3 provided the corresponding γ-hydroxy-γ-trifluoromethyl-γ-butyrolactones. The utility of these adducts was further demonstrated by treatment with Grignard reagents, leading to γ-trifluoromethylated γ-butyrolactones.

1. Introduction

Compounds bearing fluorine atoms have been extensively applied in a variety of fields including agrochemistry, pharmaceutical chemistry and materials sciences. In particular, trifluoromethyl group (CF_3) is considered as an important fluorinated motif which is commonly found in useful organic molecules. Therefore, the development of efficient methodology for the introduction of trifluoromethyl group into organic molecules has attracted considerable attention in synthetic community. A number of strategies developed for trifluoromethylation processes have been reported [1]. Among those, fluoride-catalyzed nucleophilic trifluoromethylation by using (trifluoromethyl)trimethylsilane (CF_3SiMe_3, Ruppert–Prakash reagent) [2] has emerged as a general protocol. While various electrophiles [3], *e.g.*, carbonyl compounds, esters, imines, enones, and cyclic amides were reported to react with CF_3SiMe_3, the reaction with anhydrides has only been scarcely reported in the literature. Recently, we reported fluoride-catalyzed nucleophilic addition of difluoro(phenylsulfanyl)trimethylsilane ($PhSCF_2SiMe_3$) to various anhydrides providing a general entry to γ-difluoromethylated γ-lactams [4]. We therefore envisioned that CF_3SiMe_3 would also undergo fluoride-catalyzed nucleophilic addition with anhydrides to provide the γ-hydroxy-γ-trifluoromethyl-γ-butyrolactones, which could be employed as intermediates for the preparation of γ-trifluoromethylated γ-butyrolactones as shown in Scheme 1.

2. Results and discussion

Our optimization began with the fluoride-catalyzed trifluoromethylation of CF_3SiMe_3 with phthalic anhydride. It was found that the reaction of phthalic anhydride with CF_3SiMe_3 (2 equiv.) and 10 mol% of TBAT (tetrabutylammonium triphenyldifluorosilicate) in THF at 0 to 10 °C for 4 h followed by quenching with H_2O provided the expected γ-hydroxy-γ-trifluoromethyl-γ-butyrolactone **1** in 91–95% yields. Similarly, the nucleophilic addition of CF_3SiMe_3 with succinic anhydride also readily proceeded, yielding the corresponding adduct **2** albeit in moderate yield (67% yield) (Scheme 1). Having succeeded in preparing compounds **1** and **2**, we next investigated their reactions with the Grignard reagents, expecting to obtain the corresponding γ-trifluoromethylated γ-butyrolactones **3**. Thus, treatment of **1** with 5 equiv. of CH_3MgCl in THF at 0 °C for 40 min followed by acidic work-up and treatment of the resulting crude product with a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) in CH_2Cl_2 under reflux overnight (16 h) afforded the required product **3a** in 76% yield. The formation of **3a** could be rationalized that ring-opening of compound **1** mediated by CH_3MgCl took place to give the corresponding

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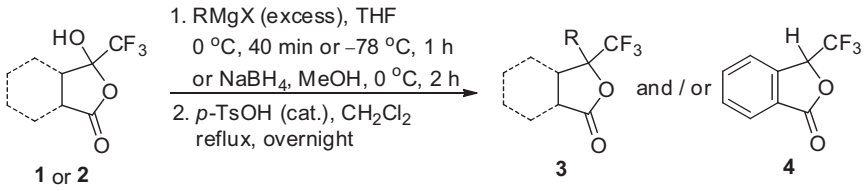
Table 1
Nucleophilic addition reactions of γ-hydroxy-γ-trifluoromethyl-γ-butyrolactones **1** or **2** with Grignard reagents.



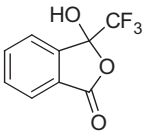
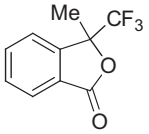
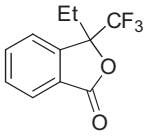
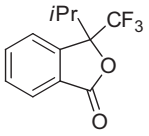
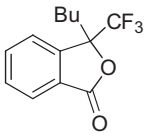
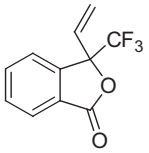
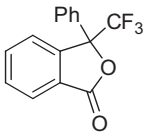
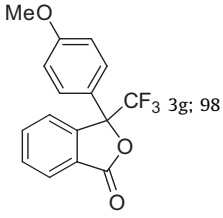
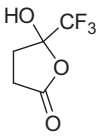
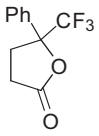
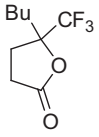
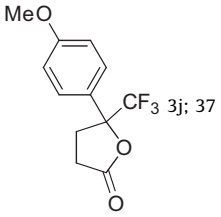
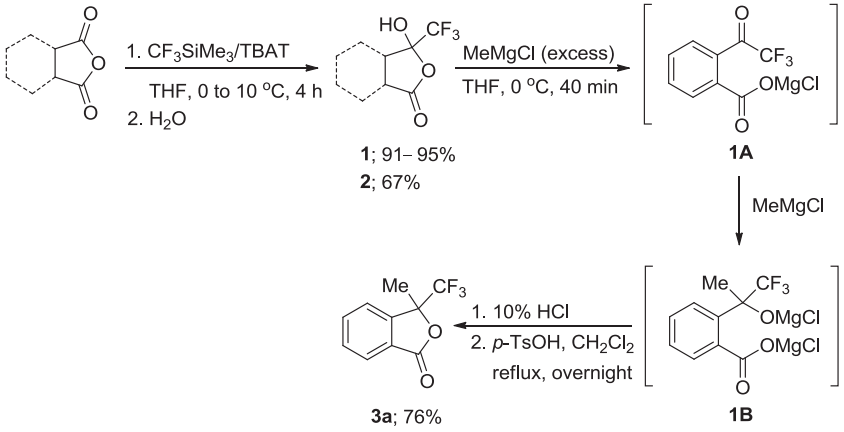
Entry	**1** or **2**	Reagent	**3**; yield (%)[a]	**4**; yield (%)[a]
1		MeMgCl	 3a; 76	–
2	**1**	EtMgCl	 3b; 23 (63)b	40 (10)[b]
3	**1**	*i*PrMgCl	 3c; 11 (34)b	50 (25)[b]
4	**1**	BuMgCl	 3d; 21 (66)b	45 (11)[b]
5	**1**	VinylMgCl	 3e; 80	–
6	**1**	PhMgCl	 3f; 99	–
7	**1**	4-MeO(Ph)MgBr	 3g; 98	–
8	**1**	$NaBH_4$	–	63
9		PhMgCl	 3h; 67	–
10	**2**	BuMgCl	 3i; 18b,c	

Table 1 (*Continued*)

Entry	**1** or **2**	Reagent	**3**; yield (%)[a]	**4**; yield (%)[a]
11	**2**	4-MeO(Ph)MgBr	 **3j**; 37	–

[a]Yields of isolated products. [b]The reaction was carried out at −78 °C for 1 h. [c]Lactonization was performed by using TFAA under reflux conditions.



Scheme 1. Trifluoromethylation of anhydrides with CF_3SiMe_3 followed by nucleophilic addition reaction with Grignard reagents.

trifluoromethyl ketocarboxylate **1A**, which subsequently reacted with a second equivalent of CH_3MgCl to provide **1B** and then **3a** after lactonization (Scheme 1).

The optimal reaction conditions were also effective for addition of other Grignard reagents to the firstly formed γ-hydroxy-γ-trifluoromethyl-γ-butyrolactone **1**. Thus, the reactions of compound **1** with vinyl-, phenyl-, and 4-methoxyphenylmagnesium reagents provided the corresponding γ-trifluoromethylated γ-butyrolactones **3e**, **3f**, and **3g** in 80%, 99%, and 98% yields, respectively, after lactonization (Table 1, entries 5–7). However, ethylmagnesium chloride, isopropylmagnesium chloride and butylmagnesium chloride reacted with compound **1**, yielding the corresponding γ-trifluoromethylated γ-butyrolactones **3b**, **3c**, and **3d** in significantly lower yields; 23%, 11%, and 21% yields, respectively. The major product obtained from each of those was found to be γ-trifluoromethylated γ-butyrolactone **4** in 40%, 50% and 45% yields, respectively (Table 1, entries 2–4). The formation of **4** can be attributed to the reduction of the intermediate **1A** by a β-hydride transfer from the Grignard reagents. Improved results were obtained when the reactions were carried out at low temperature (−78 °C) for 1 h. Under the optimized reaction conditions, the corresponding γ-trifluoromethylated γ-butyrolactones **3b**, **3c**, and **3d** were obtained in 63%, 34%, and 66% yields, together with the side product **4** in 10%, 25%, and 11% yields, respectively (Table 1, entries 2–4). It should be mentioned that the γ-trifluoromethylated γ-butyrolactone **4** was directly obtained in 63% yield from the reduction of compound **1** by using $NaBH_4$ in MeOH at 0 °C for 2 h followed by lactonization (Table 1, entry 8). Under the standard reaction conditions, γ-hydroxy-γ-trifluoromethyl-γ-butyrolactone **2** reacted with phenylmagnesium chloride, butylmagnesium chloride, and 4-methoxyphenylmagnesium bromide, to provide the desired γ-trifluoromethylated γ-butyrolactones **3h**, **3i**, and **3j**, after lactonization, in 67%, 18%, and 37% yields, respectively (Table 1, entries 9–11).

3. Conclusion

In conclusion, we have reported a fluoride-catalyzed nucleophilic addition of CF_3SiMe_3 to anhydrides to provide γ-hydroxy-γ-trifluoromethyl-γ-butyrolactones, which could be further transformed to γ-trifluoromethylated γ-butyrolactones after treatment with Grignard reagents followed by lactonization. Our developed method may be useful for synthesis of highly substituted γ-trifluoromethylated γ-butyrolactones.

4. Experimental

4.1. General information

The ^1H NMR spectra were recorded on a Bruker-400 (400 MHz) spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard. The ^{13}C NMR spectra were recorded on a Bruker 400 (100 MHz) spectrometer in $CDCl_3$ using residual non-deuterated solvent peaks as an internal standard. The ^{19}F NMR spectra were recorded on a Bruker-400 (376 MHz) spectrometer and chemical shifts (δ) were measured with fluorotrichloromethane ($\delta = 0$) as an internal standard. The IR spectra were recorded on either a Jasco A-302 or a Perkin Elmer 683 infrared spectrometer in $CHCl_3$ or neat. The electron impact mass spectra were recorded by using Thermo Finnigan Polaris Q mass spectrometer. The high resolution mass spectra were recorded on HR-TOF-MS Micromass model VQ-TOF2 mass spectrometer. Melting points were recorded on a Büchi 501 melting point apparatus and uncorrected. Tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl. Dichloromethane (CH_2Cl_2) was distilled over calcium hydride and stored over activated molecular sieves (4 Å). All glass wares and syringes were oven-dried and kept in a desiccator before use. Preparative thin-layer chromatography plates were performed by using Merck silica gel 60 PF_{254} (Art 7747). Column chromatography was performed

by using Merck silica gel 60 PF_{254} (Art 7734). Other common solvents (CH_2Cl_2, hexanes, ethyl acetate (EtOAc), methanol, and acetone) were distilled before use.

4.2. Synthesis of γ-hydroxy-γ-trifluoromethyl-γ-butyrolactones

General procedure A: a solution of (trifluoromethyl)trimethylsilane (CF_3SiMe_3, 0.6 mL, 4.0 mmol) and anhydride (2.0 mmol) in dry THF (10 mL) was treated with a solution of 10 mol% of TBAT (108 mg, 0.2 mmol) in dry THF (10 mL) at 0 °C under an argon atmosphere. The reaction mixture was stirred and kept below 10 °C for 4 h, then quenched with water and extracted with EtOAc (4× 20 mL). The combined organic phase was washed successively with water (20 mL), brine (20 mL) and dried over anhydrous Na_2SO_4. After the removal of the solvent, the crude product was purified by column chromatography (SiO_2).

4.2.1. 3-Hydroxy-3-(trifluoromethyl)isobenzofuran-1(3H)-one (**1**)

According to *the general procedure A*, the reaction of phthalic anhydride (297 mg, 2.0 mmol) and CF_3SiMe_3 (0.6 mL, 4.0 mmol) at 0 °C gave **1** (393 mg, 91% yield) as a white solid after column chromatography (SiO_2, 10–30% EtOAc in hexanes). Mp 95–96 °C (CH_2Cl_2/hexanes). IR ($CHCl_3$); ν 3152 (OH), 3032 (m), 2986 (w), 2852 (w), 1792 (s), 1607 (w), 1469 (m), 1274 (m), 1162 (m), 1145 (m), 1081 (m), 988 (s), 941 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.27–5.44 (br s, 1H, OH), 7.70–7.84 (m, 3H, 3 arom. H), 7.90 (d, $^3J_{H,H}$ = 7.6 Hz, 1H, arom. H), ^{13}C NMR (100 MHz, $CDCl_3$): δ 100.0 (q, ^2J = 36.0 Hz, C), 121.4 (q, ^1J = 284.0 Hz, CF_3), 124.0 (CH), 126.0 (CH), 126.7 (C), 132.4 (CH), 135.5 (CH), 141.8 (C), 167.3 (C). ^{19}F NMR (367 MHz, $CDCl_3$): δ −82.8 (s, 3F, CF_3). EIMS, *m/z* (rel. int.): 219 (14) $[M+H]^+$, 201 (4), 149 (100), 121 (22), 74 (13), 65 (2); HRMS (ESI-TOF), *m/z*: calcd. for $C_9H_5F_3O_3Na^+$ 241.0088 $[M+Na]^+$; found 241.0088.

4.2.2. 5-Hydroxy-5-(trifluoromethyl)dihydrofuran-2(3H)-one (**2**)

According to the general procedure A, the reaction of succinic anhydride (200 mg, 2.0 mmol) and CF_3SiMe_3 (0.6 mL, 4.0 mmol) at 0 °C gave **2** (228 mg, 67% yield) as a colorless oil after column chromatography (SiO_2, 10–80% EtOAc in hexanes). IR (neat); ν 3150 (OH), 2985 (w), 2850 (w), 1794 (s), 1605 (w), 1466 (m), 1271 (m), 1160 (m), 1147 (m), 1085 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.25–3.00 (m, 4H, $2CH_2$), 4.70–6.00 (br s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.5 (CH_2), 28.2 (CH_2), 101.5 (q, ^2J = 36.0 Hz, C), 121.7 (q, ^1J = 284.0 Hz, CF_3), 175.1 (C). ^{19}F NMR (367 MHz, $CDCl_3$): δ −85.4 (s, 3F, CF_3). EIMS, *m/z* (rel. int.): 171 (6) $[M+H]^+$, 169 (10) $[M-H]^+$, 153 (12) $[M-OH]^+$. HRMS (ESI-TOF), *m/z*: calcd. for $C_5H_4F_3O_3^+$ 169.0113 $[M-H]^+$; found 169.0107.

4.3. Synthesis of γ-trifluoromethylated γ-butyrolactones **3** and **4**

General procedure B: a solution of **1** or **2** (0.5 mmol) in dry THF (15 mL) was treated with alkyl- or arylmagnesium chloride solution (2.5 mmol) at −78 °C or 0 °C under an argon atmosphere. After stirring the reaction mixture 1 h at −78 °C, or 40 min at 0 °C, 10% HCl (2 mL) was added at −78 °C or at 0 °C. The aqueous phase was extracted with EtOAc (4× 20 mL). The combined organic phase was washed with brine (20 mL) and dried over anhydrous Na_2SO_4. After the removal of the solvent, the crude product was treated with a catalytic amount of *p*-TsOH in dry CH_2Cl_2 (12 mL) under reflux overnight (16 h) or treated with trifluoroacetic anhydride (0.5 mL) under reflux (8 h). The reaction was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (4× 10 mL). The combined organic phase was washed with brine (10 mL), and dried over anhydrous Na_2SO_4. After the removal of the solvent, the crude product was purified by column chromatography (SiO_2) or preparative thin-layer chromatography (SiO_2).

General procedure C: a solution of arylbromide (10.0 mmol) in dry THF (8 mL) was added dropwise into a suspension of Mg (turning) (0.4 g, 20.0 mmol) in dry THF (7 mL) under an argon atmosphere at room temperature. After 2 h, a solution of freshly prepared Grignard reagent was transferred dropwise *via* a canular to a solution of **1** or **2** (0.5 mmol) in THF (10 mL) at 0 °C under an argon atmosphere and then stirred for 1 h. The reaction mixture was quenched with 10% HCl (5 mL) at 0 °C and extracted with EtOAc (4× 20 mL). The combined organic phase was washed with brine (20 mL) and dried over anhydrous Na_2SO_4. After the removal of the solvent, the crude product was treated with a catalytic amount of *p*-TsOH in dry CH_2Cl_2 (12 mL) under reflux overnight (16 h). The reaction was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (4× 10 mL). The combined organic phase was washed with brine (10 mL), and dried over anhydrous Na_2SO_4. After the removal of the solvent, the crude product was purified by column chromatography (SiO_2) or preparative thin-layer chromatography (SiO_2).

4.3.1. 3-Methyl-3-(trifluoromethyl)isobenzofuran-1(3H)-one (**3a**)

According to *the general procedure B*, the reaction of **1** (110 mg, 0.5 mmol) and methylmagnesium chloride (3.0 M in THF, 0.83 mL, 2.5 mmol) at 0 °C followed by lactonization gave **3a** (83 mg, 76% yield) as a colorless oil after preparative thin-layer chromatography (SiO_2, 15% EtOAc in hexanes). IR (neat); ν 3029 (m), 3004 (w), 2947 (w), 1788 (s), 1603 (w), 1469 (m), 1319 (m), 1271 (s), 1181 (s), 1102 (m), 1076 (s), 1030 (s), 952 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.85 (s, 3H, CH_3), 7.60 (d, $^3J_{H,H}$ = 7.6 Hz, 1H, arom. H), 7.66 (t, $^3J_{H,H}$ = 7.6 Hz, 1H, arom. H), 7.77 (t, $^3J_{H,H}$ = 7.6 Hz, 1H, arom. H), 7.94 (d, $^3J_{H,H}$ = 7.6 Hz, 1H, arom. H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.7 (CH_3), 82.8 (q, ^2J = 34.0 Hz, C), 122.6 (CH), 123.5 (q, ^1J = 281.0 Hz, CF_3), 125.9 (C), 126.3 (CH), 130.9 (CH), 134.9 (CH), 145.8 (C), 168.1 (C). ^{19}F NMR (367 MHz, $CDCl_3$): δ −76.3 (s, 3F, CF_3). EIMS, *m/z* (rel. int.): 217 (6) $[M+H]^+$, 216 (11) $[M]^+$, 201 (8), 199 (100), 198 (41), 178 (26), 134 (5), 133 (7), 121 (17), 105 (7), 77 (46). HRMS (ESI-TOF), *m/z*: calcd. for $C_{10}H_7F_3O_2Na^+$ 239.0296 $[M+Na]^+$; found 239.0296.

4.3.2. 3-Ethyl-3-(trifluoromethyl)isobenzofuran-1(3H)-one (**3b**)

According to *the general procedure B*, the reaction of **1** (110 mg, 0.5 mmol) and ethylmagnesium chloride (2.0 M in THF, 1.25 mL, 2.5 mmol) at −78 °C followed by lactonization gave **3b** (73 mg, 63% yield) as a white solid together with a reduction product **4** (12 mg, 10% yield) as a colorless oil after preparative thin-layer chromatography (SiO_2, 10% EtOAc in hexanes). Mp 55–56 °C (CH_2Cl_2/hexanes). IR (CH_3Cl_3); ν 3030 (m), 2984 (m), 2944 (w), 2887 (w), 1785 (s), 1603 (m), 1469 (s), 1306 (m), 1283 (s), 1182 (s), 1083 (s), 1051 (s), 988 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.63 (t, $^3J_{H,H}$ = 7.6 Hz, 3H, CH_3), 2.19 (dq, $^2J_{H,H}$ = 14.5, $^3J_{H,H}$ = 7.3 Hz, 1H, C**H**H), 2.39 (dq, $^2J_{H,H}$ = 14.5, $^3J_{H,H}$ = 7.3 Hz, 1H, C**H**H), 7.48 (d, $^3J_{H,H}$ = 7.6 Hz, 1H, arom. H), 7.56 (t, $^3J_{H,H}$ = 7.6 Hz, 1H, arom. H), 7.70 (t, $^3J_{H,H}$ = 7.6 Hz, 1H, arom. H), 7.87 (d, $^3J_{H,H}$ = 7.6 Hz, 1H, arom. H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.7 (CH_3), 24.6 (CH_2), 86.2 (q, ^2J = 31.0 Hz, C), 122.8 (CH), 123.7 (q, ^1J = 282.0 Hz, CF_3), 126.1 (CH), 126.9 (C), 130.9 (CH), 134.9 (CH), 143.9 (C), 168.5 (C). ^{19}F NMR (367 MHz, $CDCl_3$): δ −78.7 (s, 3F, CF_3). EIMS, *m/z* (rel. int.): 231 (3) $[M+H]^+$, 204 (7), 199 (100), 161 (21), 133 (10), 121 (10), 105 (7), 77 (31). HRMS (ESI-TOF), *m/z*: calcd. for $C_{11}H_9F_3O_2Na^+$ 253.0452 $[M+Na]^+$; found 253.0452.

4.3.3. 3-Isopropyl-3-(trifluoromethyl)isobenzofuran-1(3H)-one (**3c**)

According to *the general procedure B*, the reaction of **1** (110 mg, 0.5 mmol) and isopropylmagnesium chloride (2.0 M in THF, 1.25 mL, 2.5 mmol) at −78 °C followed by lactonization gave **3c** (24 mg, 34% yield) as a colorless oil together with a reduction product **4** (25 mg, 25% yield) as a colorless oil after preparative

thin-layer chromatography (SiO_2, 15% EtOAc in hexanes). IR (CH_3Cl_3); ν 3029 (w), 2980 (w), 2928 (w), 1784 (s), 1600 (w), 1469 (m), 1250 (m), 1182 (s), 1072 (m), 1033 (m), 993 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.85, (d, $^3J_{H,H}$ = 6.8 Hz, 3H, CH_3), 0.95 (d, $^3J_{H,H}$ = 6.8 Hz, 3H, CH_3), 2.57–2.65 (sept, $^3J_{H,H}$ = 6.8 Hz, 1H, C**H**), 7.51 (d, $^3J_{H,H}$ = 7.7 Hz, 1H, arom. H), 7.56 (t, $^3J_{H,H}$ = 7.5 Hz, 1H, arom. H), 7.69 (t, $^3J_{H,H}$ = 7.5 Hz, 1H, arom. H), 7.88 (d, $^3J_{H,H}$ = 7.7 Hz, 1H, arom. H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.7 (CH_3), 16.9 (CH_3), 31.6 (CH_2), 88.5 (q, ^2J = 31.0 Hz, C), 123.1 (CH), 123.8 (q, ^1J = 282.0 Hz, CF_3), 126.2 (CH), 126.8 (C), 130.7 (CH), 134.6 (CH), 144.4 (C), 168.6 (C). ^{19}F NMR (367 MHz, $CDCl_3$): δ –73.9 (s, 3F, CF_3). EIMS, *m/z* (rel. int.): 245 (5) $[M+H]^+$, 244 (2) $[M]^+$, 202 (100), 182 (15), 175 (3), 151 (24), 133 (7), 104 (14), 77 (13). HRMS (ESI-TOF), *m/z*: calcd. for $C_{12}H_{11}F_3O_2Na^+$ 267.0609 $[M+Na]^+$; found 267.0606.

4.3.4. 3-Butyl-3-(trifluoromethyl)isobenzofuran-1(3H)-one (**3d**)

According to *the general procedure B*, the reaction of **1** (110 mg, 0.5 mmol) and butylmagnesium chloride (2.0 M in THF, 1.25 mL, 2.5 mmol) at −78 °C followed by lactonization gave **3d** (85 mg, 66% yield) as a colorless oil together with a reduction product **4** (11 mg, 11% yield) as a colorless oil in after preparative thin-layer chromatography (SiO_2, 15% EtOAc in hexanes). IR ($CHCl_3$): ν 2962 (s), 2935 (s), 2875 (m), 1789 (s), 1603 (m), 1469 (s), 1305 (m), 1261 (m), 1214 (m), 1179 (m), 1084 (m), 1059 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.64–0.78 (m, 1H, C**H**H), 0.81 (t, $^3J_{H,H}$ = 7.2 Hz, 3H, CH_3), 1.11–1.36 (m, 3H, CH_2 and C**H**H), 2.16–2.20 (m, 1H, C**H**H), 2.31–2.38 (m, 1H, C**H**H), 7.56 (d, $^3J_{H,H}$ = 7.8 Hz, 1H, arom. H), 7.66 (t, $^3J_{H,H}$ = 7.8 Hz, 1H, arom. H), 7.78 (t, $^3J_{H,H}$ = 7.8 Hz, 1H, arom. H), 7.95 (d, $^3J_{H,H}$ = 7.8 Hz, 1H, arom. H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6 (CH_3), 22.3 (CH_2), 23.8 (CH_2), 31.0 (CH_2), 85.9 (q, ^2J = 31.0 Hz, C), 122.7 (CH), 123.6 (q, ^1J = 282.0 Hz, CF_3), 126.2 (CH), 126.8 (C), 130.8 (CH), 134.9 (CH), 144.3 (C), 168.4 (C). ^{19}F NMR (367 MHz, $CDCl_3$): δ −78.8 (s, 3F, CF_3). EIMS, *m/z* (rel. int.): 258 (5) $[M]^+$, 201 (15), 189 (10), 178 (37), 175 (7), 163 (10), 155 (11), 133 (16), 107 (20), 95 (81), 81 (100), 77 (37), 67 (87), 55 (69). HRMS (ESI-TOF), *m/z*: calcd. for $C_{13}H_{13}F_3O_2Na^+$ 281.0765 $[M+Na]^+$; found 281.0765.

4.3.5. 3-(Trifluoromethyl)-3-vinylisobenzofuran-1(3H)-one (**3e**)

According to *the general procedure B*, the reaction of **1** (110 mg, 0.5 mmol) and vinylmagnesium chloride (1.6 M in THF, 1.56 mL, 2.5 mmol) at 0 °C followed by lactonization gave **3e** (91 mg, 80% yield) as a colorless oil after preparative thin-layer chromatography (SiO_2, 15% EtOAc in hexanes). IR ($CHCl_3$): ν 3075 (w), 2929 (w), 1792 (s), 1603 (m), 1469 (s), 1412 (m), 1303 (m), 1250 (m), 1183 (m), 1079 (m), 955 (m), 764 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.56 (d, $^3J_{H,H}$ = 10.8 Hz, 1H, C**H**H), 5.74 (d, $^3J_{H,H}$ = 17.1 Hz, 1H, C**H**H), 6.28 (dd, $^3J_{H,H}$ = 17.1, $^3J_{H,H}$ = 10.8 Hz, 1H, C**H**), 7.65 (d, $^3J_{H,H}$ = 7.5 Hz, 1H, arom. H), 7.69 (t, $^3J_{H,H}$ = 7.5 Hz, 1H, arom. H), 7.80 (t, $^3J_{H,H}$ = 7.5 Hz, 1H, arom. H), 7.97 (d, $^3J_{H,H}$ = 7.5 Hz, 1H, arom. H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 84.6 (q, ^2J = 33.0 Hz, C), 121.4 (CH_2), 122.8 (q, ^1J = 282.0 Hz, CF_3), 123.4 (CH), 125.5 (C), 126.5 (CH), 128.3 (CH), 131.1 (CH), 134.9 (CH), 143.9 (C), 167.9 (C). ^{19}F NMR (367 MHz, $CDCl_3$): δ −78.1 (s, 3F, CF_3). EIMS, *m/z* (rel. int.): 228 (18) $[M]^+$, 215 (15), 209 (87), 178 (97), 171 (23), 161 (35), 133 (23), 107 (14), 87 (56), 81 (76), 77 (63), 67 (87), 55 (100). HRMS (ESI-TOF), *m/z*: calcd. for $C_{11}H_7F_3O_2Na^+$ 251.0296 $[M+Na]^+$; found 251.0295.

4.3.6. 3-Phenyl-3-(trifluoromethyl)isobenzofuran-1(3H)-one (**3f**)

According to *the general procedure B*, the reaction of **1** (110 mg, 0.5 mmol) and phenylmagnesium chloride (2.0 M in THF, 1.25 mL, 2.5 mmol) at 0 °C followed by lactonization gave **3f** (142 mg, 80% yield) as a colorless oil after preparative thin-layer chromatography (SiO_2, 15% EtOAc in hexanes). IR (neat): ν 3069 (w), 1792 (s), 1600 (m), 1468 (m), 1451 (m), 1296 (m), 1281 (m), 1229 (m), 1179 (s), 1072 (s), 1025 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.41–7.50 (m, 3H, 3 arom. H), 7.69 (t, $^3J_{H,H}$ = 7.5 Hz, 1H, arom. H), 7.75–7.81 (m, 2H, 2 arom. H), 7.84 (t, $^3J_{H,H}$ = 7.5 Hz, 1H, arom. H), 7.94 (d, $^3J_{H,H}$ = 7.7 Hz, 1H, arom. H), 8.00 (d, $^3J_{H,H}$ = 7.7 Hz, 1H, arom. H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 85.6 (q, ^2J = 32.0 Hz, C), 123.2 (q, ^1J = 283.0 Hz, CF_3), 124.2 (CH), 125.9 (C), 126.5 (CH), 126.6 (CH), 128.9 (2CH), 130.0 (2CH), 131.1 (CH), 132.3 (C), 134.9 (CH), 144.9 (C), 168.0 (C). ^{19}F NMR (367 MHz, $CDCl_3$): δ −76.3 (s, 3F, CF_3). EIMS, *m/z* (rel. int.): 279 (4) $[M+H]^+$, 278 (2) $[M]^+$, 209 (100), 201 (2), 183 (3), 163 (2), 153 (15), 152 (22), 151 (5), 105 (2), 77 (4). HRMS (ESI-TOF), *m/z*: calcd. for $C_{15}H_9F_3O_2Na^+$ 301.0452 $[M+Na]^+$; found 301.0452.

4.3.7. 3-(4-Methoxyphenyl)-3-(trifluoromethyl)isobenzofuran-1(3H)-one (**3g**)

According to *the general procedure C*, the reaction of **1** (219 mg, 1.0 mmol) and 4-methoxyphenyl magnesium bromide at 0 °C followed by lactonization gave **3 g** (302 mg, 98% yield) as a colorless oil in after column chromatography (SiO_2, 5% EtOAc in hexanes). IR (neat): ν 3008 (w), 2939 (w), 2842 (w), 1790 (s), 1611 (s), 1516 (s), 1467 (s), 1261 (m), 1173 (s), 1078 (s), 1028 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.82 (s, 3H, OCH_3), 6.96 (d, $^3J_{H,H}$ = 7.9 Hz, 2H, 2 arom. H), 7.60 – 7.70 (m, 3H, 3 arom. H), 7.83 (t, $^3J_{H,H}$ = 7.4 Hz, 1H, arom. H), 7.91 (d, $^3J_{H,H}$ = 7.4 Hz, 1H, arom. H), 7.99 (d, $^3J_{H,H}$ = 7.4 Hz, 1H, arom. H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3 (OCH_3), 85.5 (q, ^2J = 32.0 Hz, C), 114.1 (2CH), 123.2 (q, ^1J = 282.0 Hz, CF_3), 123.9 (C), 124.1 (CH), 125.9 (C), 126.4 (CH), 128.2 (2CH), 130.9 (CH), 134.8 (CH), 144.9 (C), 160.6 (C), 168.0 (C). ^{19}F NMR (367 MHz, $CDCl_3$): δ −76.5 (s, 3F, CF_3). EIMS, *m/z* (rel. int.): 309 (5) $[M+H]^+$, 308 (15) $[M]^+$, 239 (100), 201 (4), 168 (7), 152 (8), 133 (4), 77 (3). HRMS (ESI-TOF), *m/z*: calcd. for $C_{16}H_{11}F_3O_3Na^+$ 331.0558 $[M+Na]^+$; found 331.0556.

4.3.8. 5-Phenyl-5-(trifluoromethyl)dihydrofuran-2(3H)-one (**3h**)

According to *the general procedure B*, the reaction of **2** (88 mg, 0.5 mmol) and phenylmagnesium chloride (2.0 M in THF, 1.25 mL, 2.5 mmol) at 0 °C followed by lactonization gave **3 h** (79 mg, 67% yield) as a colorless oil after preparative-thin layer chromatography (SiO_2, 40% CH_2Cl_2 in hexanes (×2)). IR (neat): ν 3067 (w), 2952 (w), 1807 (s), 1451 (m), 1281 (m), 1171 (s), 1094 (m), 1067 (m), 896 (s), 706 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.55–2.77 (m, 2H, 2C**H**H), 2.75–2.90 (m, 1H, C**H**H), 2.96–3.07 (m, 1H, C**H**H), 7.42–7.49 (m, 3H, 3 arom. H), 7.51–7.57 (m, 2H, 2 arom. H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.5 (CH_2), 29.6 (CH_2), 84.9 (q, ^2J = 31.0 Hz, C), 124.2 (q, ^1J = 282.0 Hz, CF_3), 126.2 (2CH), 128.7 (2CH), 129.6 (CH), 134.9 (C), 174.2 (C). ^{19}F NMR (367 MHz, $CDCl_3$): δ −80.0 (s, 3F, CF_3). EIMS, *m/z* (rel. int.): 229 (5) $[M-H]^+$, 209 (14), 182 (46), 166 (16), 153 (5), 77 (20), 66 (100). HRMS (ESI-TOF), *m/z*: calcd. for $C_{11}H_9F_3O_2Na^+$ 253.0452 $[M+Na]^+$; found 253.0453.

4.3.9. 5-Butyl-5-(trifluoromethyl)dihydrofuran-2(3H)-one (**3i**)

According to *the general procedure B*, the reaction of **2** (174 mg, 1.0 mmol) and butylmagnesium chloride (2.0 M in THF, 2.50 mL, 5.0 mmol) at −78 °C followed by lactonization with TFAA (0.5 mL) under reflux overnight (16 h) gave **3i** (37 mg, 18% yield) as a colorless oil after column chromatography (SiO_2, 5% EtOAc in hexanes). IR (neat): ν 2962 (s), 2935 (s), 2876 (m), 1799 (s), 1470 (m), 1171 (s), 1128 (m), 1035 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.84–1.00 (m, 3H, CH_3), 1.30–1.48 (m, 4H, $2CH_2$), 1.71–1.84 (m, 1H, C**H**H), 1.91–2.04 (m, 1H, C**H**H), 2.15–2.28 (m, 1H, C**H**H), 2.43 (m, 1H, C**H**H), 2.61 (m, 1H, C**H**H), 2.73 (m, 1H, C**H**H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8 (CH_3), 22.7 (CH_2), 24.1 (CH_2), 25.5 (CH_2), 27.9 (CH_2), 32.8 (CH_2), 84.6 (q, ^2J = 29.0 Hz, C), 125.1 (q, ^1J = 282.3 Hz, CF_3), 175.0 (C). ^{19}F NMR (367 MHz, $CDCl_3$): δ −81.2 (s, 3F, CF_3). EIMS, *m/z* (rel. int.): 211 (55) $[M+H]^+$, 153 (43), 141 (44), 97 (84), 55 (100). HRMS (ESI-TOF), *m/z*: calcd. for $C_9H_{13}F_3O_2Na^+$ 233.0765 $[M+Na]^+$; found 233.0764.

*4.3.10. 5-(4-Methoxyphenyl)-5-(trifluoromethyl)dihydrofuran-2(3H)-one (**3j**)*

According to *the general procedure C*, the reaction of **2** (85 mg, 0.5 mmol) and 4-methoxyphenyl magnesium bromide at 0 °C followed by lactonization gave **3j** (49 mg, 37% yield) as a colorless oil after preparative-thin layer chromatography (SiO_2, 40% CH_2Cl_2 in hexanes (×2)). IR (neat): ν 3006 (w), 2962 (w), 2843 (w), 1806 (s), 1614 (m), 1516 (s), 1464 (w), 1256 (m), 1175 (s), 1078 (m), 996 (m), 899 (m), 832 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.46–2.60 (m, 1H, C**H**H), 2.65–2.80 (m, 1H, C**H**H), 2.82–2.95 (m, 1H, C**H**H), 3.76 (s, 3H, OCH_3), 6.88 (d, $^3J_{H,H}$ = 8.8 Hz, 2H, 2 arom. H), 7.36 (d, $^3J_{H,H}$ = 8.8 Hz, 2H, 2 arom. H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 84.8 (q, ^2J = 31.0 Hz, C), 114.0 (2CH), 124.2 (q, ^1J = 281.7 Hz, CF_3), 126.7 (C), 127.6 (2CH), 160.5 (C), 174.3 (C). ^{19}F NMR (367 MHz, $CDCl_3$): δ −80.3 (s, 3F, CF_3). EIMS, *m/z* (rel. int.): 260 (27) $[M]^+$, 191 (100), 163 (18), 135 (44). HRMS (ESI-TOF), *m/z*: calcd. for $C_{12}H_{11}F_3O_2Na^+$ 283.0558 $[M+Na]^+$; found 283.0558.

*4.3.11. 3-(Trifluoromethyl)isobenzofuran-1(3H)-one (**4**)*

To the reaction mixture of **1** (61 mg, 0.28 mmol) in dry MeOH (1 mL) was added $NaBH_4$ (53 mg, 1.4 mmol) as a portionwise at 0 °C. After 2 h, the reaction mixture was quenched with 10% HCl at 0 °C then the solvents were removed by *vacuo*. The resulting mixture was extracted with EtOAc (4 × 5 mL). The combined organic phase was washed successively with water (10 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. After the removal of the solvent, the crude product was lactonized by using a catalytic amount of *p*-TsOH in dry CH_2Cl_2 (10 mL) under reflux overnight. The reaction mixture was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (4 × 10 mL), brine (10 mL), and dried over anhydrous Na_2SO_4. After the removal of the solvent, the crude product was purified by preparative thin-layer chromatography (20% EtOAc in hexanes) to give **4** (35 mg, 63% yield) as a colorless oil. IR (neat): ν 3030 (w), 2928 (w), 2855 (w), 1791 (s), 1603 (w), 1361 (m), 1296 (m), 1270 (s), 1181 (s), 1145 (s), 1039 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.64 (q, $^3J_{H,F}$ = 5.7 Hz, 1H, CH), 7.60 (d, $^3J_{H,H}$ = 7.5 Hz, 1H, arom. H), 7.63 (t, $^3J_{H,H}$ = 7.5 Hz, 1H, arom. H), 7.73 (t, $^3J_{H,H}$ = 7.5 Hz, 1H, arom. H), 7.92 (d, $^3J_{H,H}$ = 7.5 Hz, 1H, arom. H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 76.0 (q, ^2J = 35.4 Hz, C), 122.2 (q, ^1J = 278.7 Hz, CF_3), 123.5 (CH), 125.8 (C), 126.1 (CH), 131.1 (CH), 134.9 (CH), 140.5 (C), 168.3 (C). ^{19}F NMR (367 MHz, $CDCl_3$): δ −76.7 (s, 3F, CF_3). EIMS, *m/z* (rel. int.): 203 (9) $[M+H]^+$, 199 (82), 183 (19), 178 (47), 143 (45), 133 (17), 126 (20), 105 (17), 97 (46), 87 (100), 77 (54), 67 (61), 55 (97). HRMS (ESI-TOF), *m/z*: calcd. for $C_9H_5F_3O_2Na^+$ 225.0139 $[M+Na]^+$; found 225.0132.

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