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Direct conversion of primary and secondary carboxylic acids to trifluoromethyl ketones

Jonathan T. Reeves,* Fabrice Gallou, Jinhua J. Song, Zhulin Tan, Heewon Lee, Nathan K. Yee and Chris H. Senanayake

Department of Chemical Development, Boehringer Ingelheim Pharmaceuticals, Inc., 900 Old Ridgebury Road, PO Box 368, Ridgefield, CT 06877-0368, USA

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Abstract—Primary and secondary carboxylic acids were converted in one step to the corresponding trifluoromethyl ketones by treatment with trifluoroacetic anhydride (TFAA) and pyridine in toluene at 60–100 °C followed by hydrolysis/decarboxylation with water at 45 °C.

1. Introduction

Trifluoromethyl ketones are important components of many biologically active compounds.[1] The powerful inductive electron-withdrawing effect of the trifluoromethyl group renders these ketones exceptionally electrophilic, and the propensity of trifluoromethyl ketones to form stable hydrates and related tetrahedral adducts has been exploited in the design of numerous enzyme inhibitors.[2] Trifluoromethyl ketones are also valuable intermediates for the synthesis of trifluoromethyl-substituted heterocycles and other compounds.[1]

Recently, we required a practical method for large-scale preparation of primary and secondary (α-enolizable) trifluoromethyl ketones. Among numerous reported procedures for the synthesis of these compounds,[3] the method of Zard and co-workers was most attractive in terms of simplicity and potential scalability.[4] This method involves treatment of primary acid chlorides with trifluoroacetic anhydride (TFAA, 6 equiv) and pyridine (8 equiv) in dichloromethane (CH_2Cl_2) at rt and subsequent hydrolysis/decarboxylation on addition of water to give the corresponding trifluoromethyl ketones in 40–86% yield. While this procedure worked well for unhindered primary acid chlorides (RCH_2CH_2COCl), we observed very low yields for sterically demanding primary acid chlorides, such as 1-adamantane acetyl chloride (**1a**; entry 1, Table 1) even after extended reaction times. On hydrolytic work-up (H_2O, 0–20 °C), the desired ketone **2** was isolated in <5% yield, while carboxylic acid **1b** was isolated in >80% yield. In an attempt to obtain higher conversion, we heated the reaction mixture at reflux (40 °C, 48 h) followed by hydrolysis/decarboxylation at 40 °C for 2 h. Although Zard and co-workers noted the hydrolysis/decarboxylation stage of the reaction was spontaneous for unhindered substrates, we found heating for 1–2 h proved necessary for more hindered substrates to effect a complete conversion of intermediates to product. This procedure gave an improved, albeit still low yield of **2** (entry 2, 31%). A brief screen of higher boiling alternative solvents showed methyl *tert*-butyl ether (MTBE) and toluene performed equally well as CH_2Cl_2. Toluene was selected for optimization studies due to its higher boiling point and desirable process safety attributes. Heating **1a** in toluene with TFAA/pyridine at 60 °C for 2 h followed by the addition of H_2O at 0 °C and further heating at 45 °C for 2 h gave **2** in 80% yield (entry 3).

Having identified a modified procedure which allowed for the conversion of sterically hindered primary acid chlorides to trifluoromethyl ketones, we were curious if these reaction conditions could effect the conversion of carboxylic acids *directly* to trifluoromethyl ketones, thereby eliminating the need for acid chloride formation.

Keywords: Trifluoromethyl ketones; Carboxylic acids; Trifluoroacetic anhydride; Decarboxylation.
* Corresponding author. Tel.: +1 203 778 7703; fax: +1 203 791 6130; e-mail: jreeves@rdg.boehringer-ingelheim.com

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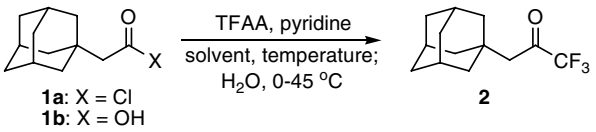
Table 1. Optimization of reaction conditions for the synthesis of **2**



Entry	Substrate	Solvent	Temperature (°C)	Time (h)	Hydrolysis temperature[c] (°C)	Yield[d] (%)
1[a]	**1a**	CH_2Cl_2	20	48	0	<5
2[a]	**1a**	CH_2Cl_2	40	48	40	31
3[a]	**1a**	PhMe	60	2	45	80
4[a]	**1b**	PhMe	60	6	45	84
5[b]	**1b**	PhMe	60	8	45	82

[a] 6 equiv TFAA, 8 equiv pyridine.
[b] 4.5 equiv TFAA, 6 equiv pyridine.
[c] H_2O added at 0 °C, then reaction held at listed temperature for 2 h.
[d] Isolated yield after chromatography on SiO_2.

Zard and co-workers postulate the reaction of acid chlorides as proceeding through trifluoroacetylation of ketene-derived pyridinium enolate **C** (Fig. 1). We reasoned that treatment of carboxylic acid **A** with TFAA/pyridine should generate mixed anhydride **B**, which could also form **C** under the reaction conditions. Notably, Zard and co-workers reported a single example of conversion of a sodium carboxylate salt to a trifluoromethyl ketone, which likewise should proceed through the intermediacy of **B** and **C**.[4a,b] Indeed, the subjection of 1-adamantane acetic acid (**1b**) to the optimized reaction conditions employed for the corresponding acid chloride **1a** gave **2** in 84% yield (entry 4) after 6 h. Furthermore, we found that the stoichiometry of the reagent system could be reduced to 4.5 equiv TFAA and 6 equiv pyridine (from 6 equiv/8 equiv, respectively) with only a moderate increase in reaction time and no significant decrease in the yield (entry 5).

Table 2 presents a survey of the scope of the reaction. Primary carboxylic acids converted smoothly to trifluoromethyl ketones (entries 1–3). The indole N–H functionality could be carried through the reaction (entry 3), presumably undergoing N-trifluoroacetylation in the first stage of the reaction and subsequent cleavage during the hydrolysis/decarboxylation stage. We also found that secondary carboxylic acids could be converted to the corresponding trifluoromethyl ketones (entries 4–8). This transformation was not possible using the procedure of Zard and co-workers.[4a,b] Higher temperatures (75–100 °C) and longer reaction times were necessary, however, for the conversion of secondary carboxylic acids.

In conclusion, we have described a simple procedure for the direct conversion of primary and secondary carboxylic acids to trifluoromethyl ketones. The process reported here eliminates the need for an additional step for the conversion of carboxylic acids to acid chlorides prior to trifluoromethyl ketone formation. In addition, these conditions allow for the successful reaction of substrates which give low yields (hindered primary substrates) or no reaction (secondary substrates) using the previously described procedure for acid chlorides.[4a,b] The use of inexpensive reagents and readily available, easily handled carboxylic acids as starting materials makes this a practical method for accessing enolizable trifluoromethyl ketones.

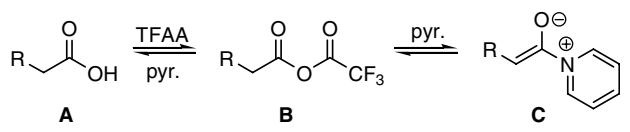


Figure 1. Mixed anhydride pathway to pyridinium enolate **C**.

2. Experimental

2.1. General procedure

A solution of carboxylic acid (10.0 mmol) in toluene (25 mL) was treated at rt with TFAA (6.3 mL, 45.0 mmol, 4.5 equiv). The reaction mixture was cooled to 0–5 °C and treated slowly with pyridine (4.9 mL, 60.0 mmol, 6.0 equiv). The reaction mixture was then heated at the required temperature (see Table 2) until starting material was consumed by HPLC or GC analysis. The reaction mixture was cooled to 0 °C, water (20 mL) was slowly added, and the reaction mixture was heated at 45 °C for 2 h. After cooling to rt, the layers were cut, the aqueous phase extracted with MTBE, and the combined organic layers washed with 1 N NaOH solution, dried over $MgSO_4$, filtered, and concentrated to give the crude product, which was purified by chromatography on silica gel.

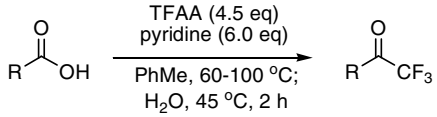
2.2. 3-Adamantan-1-yl-1,1,1-trifluoropropan-2-one (2)

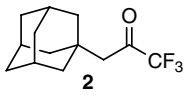
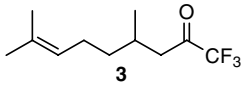
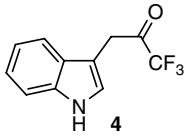
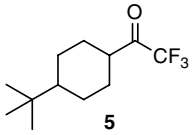
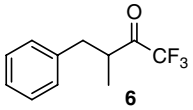
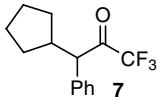
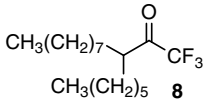
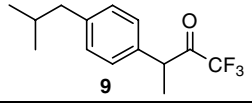
Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 2H), 1.99 (br s, 3H), 1.73–1.64 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6 (q, $J = 35$ Hz), 115.1 (q, $J = 291$ Hz), 48.8, 42.0, 36.5, 34.0, 28.5; HRMS calcd for $C_{13}H_{16}F_3O$ $[M-H]^+$: 245.1147; found: 245.1163.

2.3. 1,1,1-Trifluoro-4,8-dimethylnon-7-en-2-one (3)

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.10–5.06 (m, 1H), 2.70 (dd, 1H, $J = 17.9$, 5.5 Hz), 2.53 (dd, 1H, $J = 17.9$, 7.9 Hz), 2.16–2.08 (m, 1H), 2.05–1.94 (m, 2H), 1.69 (s, 3H), 1.60 (s, 3H), 1.41–1.23 (m, 2H), 0.96

Table 2. Conversion of carboxylic acids to trifluoromethyl ketones



Entry	Product	Temperature (°C)	Time (h)	Yield[a] (%)
1	 **2**	60	8	82
2	 **3**	60	7	55
3	 **4**	60	6	78
4	 **5**	75	24	63[c]
5	 **6**	100[b]	48	58[d]
6	 **7**	100[b]	30	52
7	 **8**	100[b]	48	41
8	 **9**	60	8	66

[a] Isolated yield after chromatography on SiO_2.
[b] Reaction heated at 60 °C for 1 h, then at 100 °C for indicated time.
[c] Ratio of 1,4-*anti*:1,4-*syn* = 2.2:1.
[d] For previous synthesis of **6**, see Ref. 3a.

(d, 3H, $J = 6.7$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.2 (q, $J = 34$ Hz), 132.0, 123.7, 115.5 (q, $J = 290$ Hz), 43.4, 36.5, 27.8, 25.6, 25.3, 19.4, 17.6; HRMS calcd for $C_{11}H_{16}F_3O$ $[M-H]^+$: 221.1153; found: 221.1171.

2.4. 1,1,1-Trifluoro-3-(1*H*-indol-3-yl)propan-2-one (4)

Tan solid; mp (hexanes/EtOAc) 66–70 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (br s, 1H), 7.50 (d, 1H, $J = 8.0$ Hz), 7.37 (d, 1H, $J = 8.1$ Hz), 7.25–7.21 (m, 1H), 7.18–7.14 (m, 2H), 4.17 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.9 (q, $J = 34$ Hz), 136.0, 126.9, 123.9, 122.7, 120.2, 118.3, 115.9 (q, $J = 291$ Hz), 111.4, 104.6, 33.3; HRMS calcd for $C_{11}H_9F_3NO$ $[M+H]^+$: 228.0630; found: 228.0652.

2.5. 1-(4-*tert*-Butylcyclohexyl)-2,2,2-trifluoroethanone (5)

Major diastereomer (1,4-*anti*): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.08–3.05 (m, 1H), 2.21 (d, 2H, $J = 13.6$ Hz), 1.70–1.56 (m, 4H), 1.23–1.12 (m, 2H), 1.04–0.97 (m, 1H), 0.83 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.2 (q, $J = 32$ Hz), 115.6 (q, $J = 293$ Hz), 47.7, 41.0, 32.3, 27.3, 26.6, 23.2; GC–MS: 236 $[M]^+$, 57. Minor diastereomer (1,4-*syn*): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.77–2.69 (m, 1H), 2.03 (d, 2H, $J = 12.7$ Hz), 1.93–1.90 (m, 2H), 1.46–1.37 (m, 2H), 1.13–1.02 (m, 3H), 0.86 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.6 (q, $J = 33$ Hz), 115.8 (q, $J = 292$ Hz), 47.0, 45.2, 32.4, 28.4, 27.3, 26.3; GC–MS: 236 $[M]^+$, 57.

2.6. 1,1,1-Trifluoro-3-methyl-4-phenylbutan-2-one (6)[3a]

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.27 (m, 2H), 7.24–7.20 (m, 1H), 7.15–7.13 (m, 2H), 3.28–3.21 (m, 1H), 3.10 (dd, 1H, $J = 13.7$, 6.4 Hz), 2.64 (dd, 1H, $J = 13.7$, 7.9 Hz), 1.19 (d, 3H, $J = 6.9$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.7 (q, $J = 33$ Hz), 137.9, 128.6, 128.2, 126.8, 115.7 (q, $J = 292$ Hz), 42.9, 36.9, 15.9; GC–MS: 216 $[M]^+$, 91.

2.7. 3-Cyclopentyl-1,1,1-trifluoro-3-phenylpropan-2-one (7)

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.14 (m, 5H), 3.73 (d, 1H, $J = 10.9$ Hz), 2.62–2.52 (m, 1H), 1.88–1.80 (m, 1H), 1.64–1.48 (m, 3H), 1.44–1.28 (m, 2H), 1.10–1.02 (m, 1H), 1.00–0.93 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.7 (q, $J = 33$ Hz), 135.5, 128.8, 128.3, 127.9, 115.8 (q, $J = 292$ Hz), 58.9, 43.1, 31.5, 30.6, 25.1, 24.5; GC–MS: 256 $[M]^+$, 188, 159, 91.

2.8. 1,1,1-Trifluoro-3-hexylundecan-2-one (8)

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.95–2.88 (m, 1H), 1.75–1.68 (m, 2H), 1.53–1.46 (m, 2H), 1.30–1.22 (m, 20H), 0.89–0.86 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.6 (q, $J = 33$ Hz), 115.6 (q, $J = 291$ Hz), 46.5, 31.8, 31.5, 31.2, 31.1, 29.5, 29.3, 29.2, 29.1, 27.1, 27.0, 22.6, 22.5, 14.1, 14.0.

2.9. 1,1,1-Trifluoro-3-(4-*iso*-butylphenyl)butan-2-one (9)

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15–7.12 (m, 4H), 4.16 (q, 1H, $J = 6.9$ Hz), 2.45 (d, 2H, $J = 7.2$ Hz), 1.84 (m, 1H), 1.50 (d, 3H, $J = 6.9$ Hz), 0.89 (d, 6H, $J = 6.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.1 (q, $J = 33$ Hz), 141.7, 134.0, 129.9, 127.7, 115.9 (q, $J = 292$ Hz), 46.9, 45.0, 30.2, 22.3, 17.9; GC–MS: 258 $[M]^+$, 215, 161.

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