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Trifluoroacetic Anhydride as an Activator in the Acylation of Aryl Methyl Ketones with Carboxylic Acids

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Abstract—Trifluoroacetic anhydride was used as an efficient activator of the acylation of aryl methyl ketones with carboxylic acids in the presence of Brønsted and Lewis acids (SF_3SO_3H, $MeSO_3H$, 4-$MeC_6H_4SO_3H\cdot H_2O$, $BF_3\cdot Et_2O$). In all cases, the products were the corresponding β-diketones. In the reactions in the presence of boron trifluoride–diethyl ether complex, the products were isolated as BF_2-chelates with high yields.

Keywords: 1,3-diketones, acylation, trifluoroacetic anhydride, carboxylic acids, aryl methyl ketones, acid catalysis

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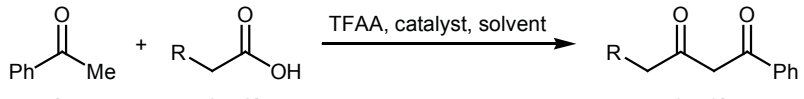
β-Dicarbonyl compounds constitute one of the most important classes of organic compounds and are widely used as key building blocks in organic synthesis. They also exhibit various kinds of biological activity, including antitumor, antiviral, anti-inflammatory, antioxidant, and antimicrobial activities, as well as a broad spectrum of ionophoric properties [1–4].

We previously reported [5] for the first time the synthesis of β-keto acids directly from carboxylic acids without preliminary activation of the latter. Carboxylic acids containing branched alkyl groups [such as 3.3-dimethylbutanoic, 2-methylbutanoic, and 2-(adamantan-1-yl)acetic acids] in the system trifluoroacetic anhydride (TFAA)/trifluoromethanesulfonic acid undergo self-acylation to produce the corresponding β-dicarbonyl compounds. Trifluoroacetic anhydride readily reacts with carboxylic acids to give mixed anhydrides, acyl trifluoroacetates, thus playing the role of an activatng agent. Trifluoromethanesulfonic acid used as catalyst favors enolization of carbonyl compounds and enhances the acylating activity of acyl trifluoroacetates. Using the system TFAA/CF_3SO_3H we have developed a simple and efficient procedure for the preparation of β-diketones widely needed in organic synthesis and synthesized heterocyclic compounds from arenes and carboxylic acids by one-pot reactions [6, 7].

The goal of the present work was to find out whether TFAA can be used as an activating agent in the synthesis of β-diketones in the presence of other acid catalysts that are more accessible than trifluoromethanesulfonic acid. The substrates were aromatic methyl ketones: acetophenone (**1a**) and 2-acetylthiophene (**1b**). Apart from CF_3SO_3H, Brønsted acids, namely methanesulfonic acid ($MeSO_3H$) and *p*-toluenesulfonic acid ($TsOH\cdot H_2O$), and a Lewis acid, boron trifluoride–diethyl ether complex ($BF_3\cdot Et_2O$) were used as catalysts.

Acetophenone (**1a**) reacted with 3.3-dimethylbutanoic acid (**2a**) in TFAA in the presence of $MeSO_3H$ or $TsOH\cdot H_2O$ (reactant molar ratio **1a**–**2a**–TFAA–catalyst = 1:1:6:1) to give β-diketone **3a**, as in the presence of trifluoromethanesulfonic acid [6] (Scheme 1). The maximum yields of **3a** were achieved after heating the reactants for 4-h in boiling nitromethane in the presence of $MeSO_3H$ (60–65%) or $TsOH\cdot H_2O$ (57–60%). For comparison, the yield of **3a** in the reaction cata-

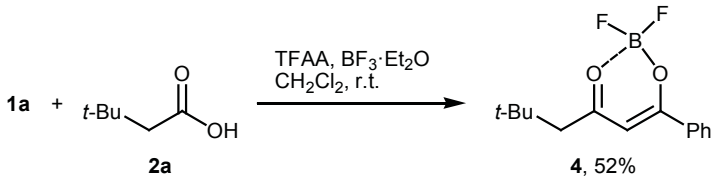
Scheme 1.



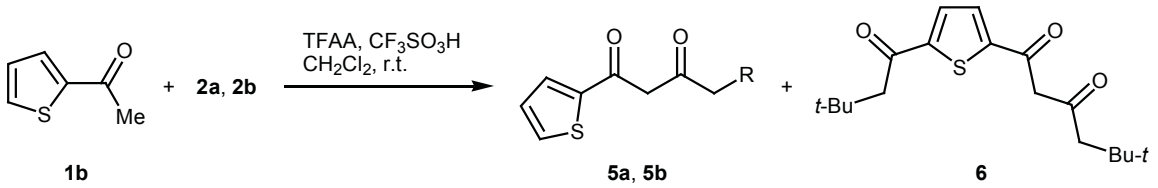
1a **2a**, **2b** **3a**, **3b**

R = *t*-Bu (**a**), 1-Ad (**b**); Catalyst = CF_3SO_3H, $MeSO_3H$, $TsOH\cdot H_2O$; solvent: CH_2Cl_2, $MeNO_2$.

Scheme 2.



Scheme 3.



R = *t*-Bu (**a**), 1-Ad (**b**); reaction conditions: ratio **1b**–**2**–TFAA–CF_3SO_3H 1:1:6:1, reaction time 22 h (*a*); 1:1:3:1, 48 h (*b*); 1:1:1.5:1, 24 h (*c*); 1:2:3:1, 24 h (*d*).

lyzed by CF_3SO_3H (CH_2Cl_2, room temperature, 2–4 h) was 70%. In the reactions catalyzed by $MeSO_3H$ at room temperature (3 days), the yields of β-diketone **3a** were lower, 35% in CH_2Cl_2 and 23% in $MeNO_2$. A similar reaction of acetophenone with 2-(adamantan-1-yl)acetic acid (**2b**) in nitromethane in the presence of $MeSO_3H$ gave 25% of adamantyl-containing β-diketone **3b** after 2 h under reflux, though the yield of **3b** in the presence of trifluoromethanesulfonic acid was almost twice as high (47%) [6].

The acylation of acetophenone (**1a**) with 2,2-dimethylbutanoic acid (**2a**) in TFAA in the presence of $BF_3·Et_2O$ was quite efficient. After 48 h at room temperature (ratio **1a**–**2a**–TFAA–catalyst = 1:1:3:1), the corresponding diketone was formed with a high yield and was isolated as boron chelate **4** (Scheme 2).

The acylation of acetylthiophene (**1b**) with 3,3-dimethylbutanoic acid (**2a**) in TFAA has not been studied previously. We were the first to carry out this reaction in the presence of trifluoromethanesulfonic acid as acylation catalyst. It was found that the major product in the reaction of equimolar amounts of **1b**, **2a**, and CF_3SO_3H was β-diketone **5a** (yield 56–60%; Scheme 3, *a*–*c*) and that 3 equiv of TFAA was sufficient. When 2 equiv of **2a** was used, the yield of **5a** reached 90% (Scheme 3, *d*). 2,5-Disubstituted thiophene **6** containing mono- and β-dicarbonyl substituents was also formed as minor product whose yield did not exceed 5%. In the reaction of **1b** with 2-(adamantan-1-yl)acetic acid (Scheme 3, *c*, 24 h), the only product was adamantyl-containing β-diketone **5b**; its yield (80%) was significantly higher than in the presence of 0.5 equiv of trifluoromethanesulfonic acid [6].

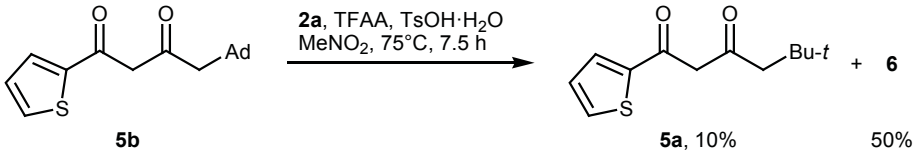
Table 1 shows the results obtained in the reaction of α-acetylthiophene (**1b**) with 3,3-dimethylbutanoic acid in TFAA in the presence of $MeSO_3H$, $TsOH·H_2O$, and

Table 1. Reaction of α-acetylthiophene (**1b**) with 3,3-dimethylbutanoic acid (**2a**) in TFAA in the presence of $MeSO_3H$, $TsOH·H_2O$, and $BF_3·Et_2O$[a]

Entry no.	Catalyst	Solvent	Temperature, °C	Reaction time, h	Yield,[b] %		
					5a	**6**	**2a**
1	$MeSO_3H$	CH_2Cl_2	Reflux	3	Traces	Traces	90
2	$TsOH·H_2O$	CH_2Cl_2	Reflux	3	28	20	40
3	$MeSO_3H$	$MeNO_2$	75	4	28	13	
4	$TsOH·H_2O$	$MeNO_2$	75	4	23	7	18
5	$TsOH·H_2O$	CH_2Cl_2	Room temperature	48	32	3	23
6[c]	$BF_3·Et_2O$	CH_2Cl_2	Room temperature	96	60[d]		

[a] Amounts of reactants: **1b**, 1 mmol; **2a**, 1 mmol; TFA, 6 mmol; catalyst, 1 mmol.
[b] Isolated yield based on the initial ketone.
[c] 3 equiv of TFAA was used.
[d] The product was isolated as BF_2 chelate **7** (Fig. 1).

Scheme 4.



$BF_3·Et_2O$. It is seen that replacement of fairly expensive CF_3SO_3H by more accessible $MeSO_3H$ and *p*-toluenesulfonic acid did not change the reaction direction. Under the given conditions (Table 1, entry nos. 1–5), the major product was (as before) β-diketone **5a**. However, the yield of **5a** did not exceed 35% based on the initial acetylthiophene. Nevertheless, the synthesis of **5a** in the presence of TsOH as a cheap catalyst (3 equiv of TFAA, room temperature; Table 1, entry no. 5) seems fairly promising.

Our results suggest higher reactivity of the CH_3CO group than of the 5-position of the thiophene ring in the initial ketone; furthermore, elevated temperature favors formation of disubstituted thiophene **6**. Thus, the reaction of **5a** with 3,3-dimethylbutanoic acid (**2a**) in TFAA in the presence of $TsOH·H_2O$ in boiling methylene chloride afforded 40% of **6**.

An attempt to acylate adamantyl-containing β-diketone **5b** with 3,3-dimethylbutanoic acid in TFAA (**2a**–**5b**–TFAA–TsOH = 1:1:6:1) gave unexpected results. We isolated β-diketone **5a** and disubstituted thiophene **6** containing only fragments of 3,3-dimethylbutanoic acid (Scheme 4). Presumably, the reaction involves transacylation of **5b** to diketone **5a**, and the latter is acylated with 3,3-dimethylbutanoic acid. The amount of triketone **6** (50%) significantly exceeded the amount of transacylation product **5a** (10%). It should be noted that transacylation of β-diketones is well known and that this reaction is fairly general [8].

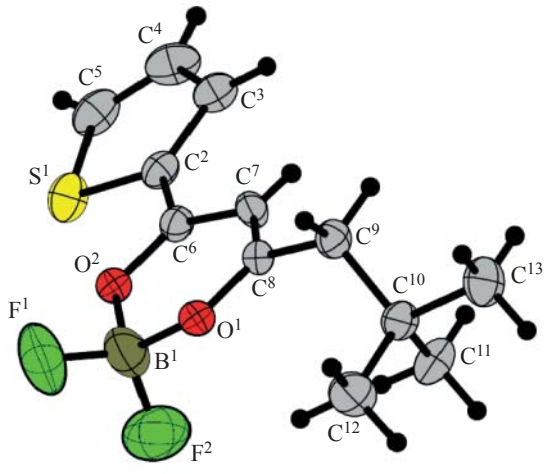


Fig. 1. Structure of the molecule of (5,5-dimethyl-1-(thiophen-2-yl)-3-oxohex-1-en-1-olato)difluoroboron (**7**) according to the X-ray diffraction data. Non-hydrogen atoms are shown with 50% probability thermal vibration ellipsoids.

The ease of formation and purification and relatively high yield of difluoroborate **7** in the presence of $BF_3·Et_2O$ as catalyst (Table 1, entry no. 6) are worth noting. In this case, no 2,5-disubstituted thiophene derivatives were formed. The structure of chelate **7** was determined by X-ray analysis (Fig. 1).

In summary, we have studied the possibility of using trifluoroacetic anhydride to activate acylation of aryl methyl ketones with carboxylic acids in the presence of some acid catalysts (CF_3SO_3H, CH_3SO_3H, *p*-$MeC_6H_4SO_3H$ H_2O, $BF_3·Et_2O$) with a view to obtaining β-diketones. It has been found that the target β-dicarbonyl compounds can be synthesized in high yields using more accessible (than previously proposed trifluoromethanesulfonic acid) methanesulfonic acid, *p*-toluenesulfonic acid, and boron trifluoride–diethyl ether complex. In the reactions catalyzed by $BF_3·Et_2O$, the products were isolated as BF_2 chelates.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer at 400 and 100 MHz, respectively, using $CDCl_3$ as solvent and reference. The X-ray diffraction data for compound **7** were obtained with a STOE diffractometer equipped with a Pilatus 100K semiconductor detector (Cu K_α radiation, λ 1.54086 Å; multilayer focusing monochromator). The data were processed using STOE X-AREA 1.67 package (STOE&Cie, Darmstadt, Germany, 2013) and LANA program included in the X-Area package to minimize differences in equivalent reflections (multiscan method). Analytical thin-layer chromatography was performed using Merck DC Alufolien Kieselgel 60 F_{254} plates; spots were visualized under UV light (λ 254 nm). Silica gel Kieselgel 40/60 (Merck) was used for preparative column chromatography. Trifluoroacetic anhydride was distilled over P_2O_5 prior to use.

General procedure for the acylation of aryl methyl ketones 1a and 1b with carboxylic acids 2a

and 2b. A mixture of reactants was kept for a required time at a required temperature (for details, see text). The mixture was treated with water and extracted with methylene chloride. The extract was washed in succession with water, a 2% solution of sodium hydrogen carbonate until weakly alkaline washings, and water until neutral washings, dried over magnesium sulfate, and evaporated. The residue was subjected to column chromatography on silica gel using methylene chloride as eluent. Boron chelates **4** and **7** were isolated by evaporation of the reaction mixture, followed by treatment of the residue with hexane. β-Diketones **3a**, **3b**, and **5b** were reported previously [6].

(5,5-Dimethyl-1-phenyl-3-oxohex-1-en-1-olato)-difluoroboron (4) was synthesized by reaction of ketone **1a** (0.120 mL, 1 mmol) with acid **2a** (0.13 mL, 1 mmol), TFAA (0.42 mL, 3 mmol), and $BF_3{\cdot}Et_2O$ (0.13 mL, 1 mmol) in 2 mL of CH_2Cl_2; room temperature, 48 h. Yield 138 mg (52%), light yellow powder, mp 118–119°C, R_f 0.70 ($CHCl_3$). ^{1}H NMR spectrum, δ, ppm: 1.04 s (9H, *t*-Bu), 2.48 s (2H, CH_2), 6.55 s (1H, CH=), 7.53 t (2H, H_{arom}, J = 7.6 Hz), 7.68 t (1H, H_{arom}, J = 7.6 Hz), 8.05 d (2H, H_{arom}, J = 7.6 Hz). ^{13}C NMR spectrum, δ_C, ppm: 29.6 [C(**C**$H_3)_3$], 33.2 [**C**$(CH_3)_3$], 51.1 (CH_2), 98.5 (CH=), 128.6 (CH_{arom}), 128.8 (CH_{arom}), 130.9 (C_{arom}), 135.0 (CH_{arom}), 181.9 (=COB), 194.4 (C=O). Found, %: C 63.51; H 6.14; F 13.88. $C_{14}H_{17}BF_2O_2$. Calculated, %: C 63.19; H 6.44; F 14.28. *M* 266.09.

5,5-Dimethyl-1-(thiophen-2-yl)hexane-1,3-dione (5a) was synthesized by reaction of **1b** (0.105 mL, 1 mmol), **2a** (0.26 mL, 2 mmol), TFAA (0.42 mL, 3 mmol), and CF_3SO_3H (0.088 mL, 1 mmol) in 2 mL of CH_2Cl_2; room temperature, 24 h. Yield 201 mg (90%), lustrous orange powder, mp 58–60°C, R_f 0.75 ($CHCl_3$). ^{1}H NMR spectrum, δ, ppm (ketone–enol ratio 4:96): enol: 1.03 s (9H, *t*-Bu), 2.09 s (2H, CH_2), 5.94 s (1H, CH=), 7.11 m (1H, H_{arom}), 7.58 d (1H, H_{arom}, J = 4.8 Hz), 7.67 d (1H, H_{arom}, J = 3.5 Hz), 15.66 br.s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 29.5 [C(**C**$H_3)_3$], 31.5 [**C**$(CH_3)_3$], 50.4 (CH_2), 97.5 (CH=), 127.8 (CH_{arom}), 129.8 (CH_{arom}), 132.1 (CH_{arom}), 142.0 (C_{arom}), 182.5 [=C(OH)], 187.4 (C=O). Found, %: C 64.47; H 7.36; S 14.39. $C_{12}H_{16}O_2S$. Calculated, %: C 64.25; H 7.19; S 14.29. *M* 224.32.

5,5-Dimethyl-1-[5-(3,3-dimethylbutanoyl)thiophen-2-yl]hexane-1,3-dione (6) was synthesized by reaction of diketone **5a** (0.22 g, 1 mmol), acid **2a** (0.26 mL, 2 mmol), TFAA (0.84 mL, 6 mmol), and $TsOH{\cdot}H_2O$ (0.19 g, 1 mmol) in 2 mL of CH_2Cl_2; reflux, 5 h. Yield 129 mg (40%), light yellow powder, mp 172–174°C, R_f 0.55 ($CHCl_3$). ^{1}H NMR spectrum, δ, ppm (ketone–enol ratio 2:98): enol: 1.05 s (9H, *t*-Bu), 1.07 s (9H, *t*-Bu), 2.25 s (2H, CH_2), 2.77 s (2H, CH_2), 6.00 s (1H, CH=), 7.65 d (2H, H_{arom}, J = 3.7 Hz). ^{13}C NMR spectrum, δ_C, ppm: 29.5 [C(**C**$H_3)_3$], 29.6 [C(**C**$H_3)_3$], 31.4 [**C**$(CH_3)_3$], 31.7 [**C**$(CH_3)_3$], 50.9 (CH_2), 51.0 (CH_2), 98.0 (CH=), 129.5 (CH_{arom}), 131.7 (CH_{arom}), 147.0 (C_{arom}), 149.2 (C_{arom}), 180.2 [=C(OH)], 190.7 (C=O), 192.7 (C=O). Found, %: C 67.33; H 8.26; S 9.56. $C_{18}H_{26}O_3S$. Calculated, %: C 67.04; H 8.13; S 9.94. *M* 322.46.

(5,5-Dimethyl-1-(thiophen-2-yl)-3-oxohex-1-en-1-olato)difluoroboron (7) was synthesized by reaction of ketone **1b** (0.105 mL, 1 mmol), acid **2a** (0.13 mL, 2 mmol), TFAA (0.42 mL, 3 mmol), and $TsOH{\cdot}H_2O$ (0.19 g, 1 mmol) in 2 mL of CH_2Cl_2; reflux, 5 h. Yield 129 mg (60%), colorless transparent crystals, mp 138–139°C, R_f 0.70 ($CHCl_3$). ^{1}H NMR spectrum, δ, ppm: 1.10 s (9H, *t*-Bu), 2.44 s (2H, CH_2), 6.31 s (1H, CH=), 7.26 m (1H, H_{arom}), 7.87 d (1H, H_{arom}, J = 4.8 Hz), 8.01 d (1H, H_{arom}, J = 3.9 Hz). ^{13}C NMR spectrum, δ_C, ppm: 29.6 [C(**C**$H_3)_3$], 33.1 [**C**$(CH_3)_3$], 50.8 (CH_2), 97.9 (CH=), 129.1 (CH_{arom}), 134.8 (CH_{arom}), 135.9 (C_{arom}), 137.2 (CH_{arom}), 175.6 [=C(OB)] 192.6 (C=O). Found, %: C 53.19; H 5.33; S 11.69. $C_{12}H_{16}O_2S$. Calculated, %: C 52.97; H 5.56; S 11.78. *M* 272.12. Crystallographic data: $C_{12}H_{16}O_2S$ (*M* 272.12); triclinic crystal system, space group *P*-1; unit cell parameters: a = 6.9641(5), b = 9.6509(7), c = 11.1094(6) Å; α = 103.362(6), β = 91.794(6), γ = 109.906(6)°; V = 678.09(9) Å^3; Z = 2; d_{calc} = 1.333 g/cm^3. The X-ray diffraction data for compound **7** were deposited to the Cambridge Crystallographic Data Centre (CCDC entry no. 1850382) and are available at www.ccdc.cam.ac.uk/data_request/cif.

CONFLICT OF INTEREST

The authors declare the absence of conflict of interest.

REFERENCES

1. Benetti, S., Romagnoli, R., De Risi, C., Spalluto, G., and Zanirato, V., *Chem. Rev*., 1995, vol. 95, p. 1065. https://doi.org/10.1021/cr00036a007
2. Kel'in, A.V., *Curr. Org. Chem*., 2003, vol. 7, p. 1691. https://doi.org/10.2174/1385272033486233
3. Vigato, P.A., Peruzzo, V., and Tamburini, S., *Coord. Chem. Rev*., 2009, vol. 253, p. 1099. https://doi.org/10.1016/j.ccr.2008.07.013

4. Shokova, E.A., Kim, D.K., and Kovalev, V.V., *Russ. J. Org. Chem*., 2015, vol. 51, p. 755. https://doi.org/10.1134/S1070428015060019
5. Kovalev, V., Shokova, E., Shmailov, A., Vatsouro, J., and Tafeenko, V., *Eur. J. Org. Chem*., 2010, vol. 2010, p. 3754. https://doi.org/10.1002/ejoc.201000312
6. Kim, J.K., Shokova, E., Tafeenko, V., and Kovalev, V., *Beilstein J. Org. Chem*., 2014, vol. 10, p. 2270. https://doi.org/10.3762/bjoc.10.236
7. Kim, J.K., Gong, M., Shokova, E.A., Tafeenko, V.A., Kovaleva, O.V., Wu, Y., and Kovalev, V.V., *Org. Biomol. Chem*., 2020, vol. 18, p. 5625. https://doi.org/10.1039/D0OB01228A
8. Katritzky, A.R., Wang, Z., Wang, M., Wilkerson, C.R., Hall, C.D., and Akhmedov, N.G., *J. Org. Chem*., 2004, vol. 69, p. 6617. https://doi.org/10.1021/jo049274l