Noncatalytic Electrophilic Alkylation of 1*H*-Indole with 2-Trifluoroacetyl-1,3-heterazoles

Pavel V. Khodakovskiy,[a,b] Pavel K. Mykhailiuk,*[a,b] Dmitriy M. Volochnyuk,[a,c] Andrey A. Tolmachev[a,b]

[a] Enamine Ltd., Oleksandra Matrosova Street 23, Kyiv 01103, Ukraine
Fax +380(44)2351273; E-mail: Pashamk@gmx.de

[b] Department of Chemistry, Kyiv National Taras Shevchenko University, Volodymyrska Street 64, Kyiv 01033, Ukraine

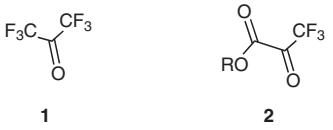
[c] Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Murmanska Street 5, 02660 Kyiv-94, Ukraine

Received 27 October 2009; revised 3 November 2009

Abstract: A set of highly electrophilic 2-trifluoroacetyl-1,3-heterazoles demonstrated excellent activity in the *C*-hydroxyalkylation of 1*H*-indole. The reaction conditions and yields of the corresponding trifluoromethyl-substituted alcohols depend strongly on the electron-withdrawing nature of the 1,3-heterazole unit.

Key words: 1,3-heterazoles, alkylations, trifluoromethyl alcohols, indoles, electrophilic additions

The trifluoromethyl group is one of the most attractive functional groups in organic chemistry because trifluoromethyl-containing molecules often possess intriguing physical and biological properties. Therefore, the incorporation of the trifluoromethyl group into organic compounds is a topic of growing interest in fluoroorganic chemistry, and many corresponding synthetic strategies have been elaborated.[1] Commercially available trifluoromethyl ketones hexafluoroacetone (**1**) and trifluoropyruvates **2** are highly valuable building blocks commonly used as sources of the trifluoromethyl group to prepare trifluoromethyl-containing compounds (Figure 1).[2] However, although the chemical reactivity of both compounds **1** and **2** has been thoroughly studied,[3] little is known of the chemistry of other trifluoromethyl ketones.[4]

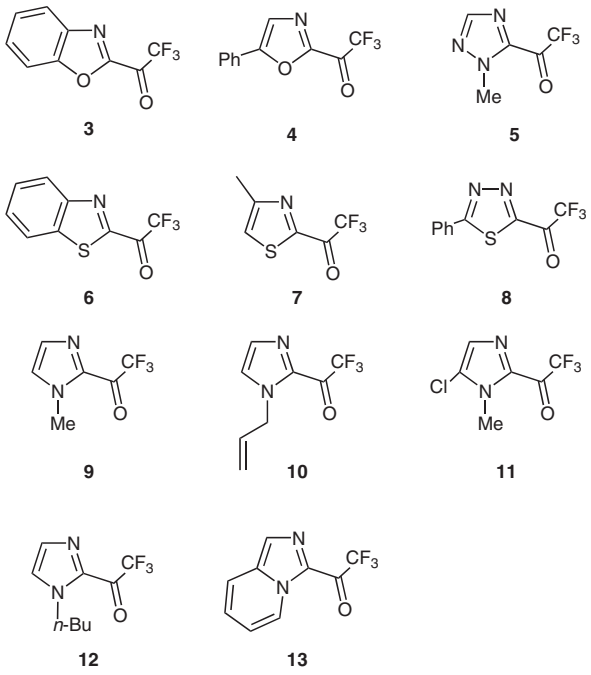


1 2

Figure 1 Common and highly usable trifluoromethyl ketones: hexafluoroacetone (**1**) and trifluoropyruvates **2**

Recently, we started a project aimed at the preparation and application of various (trifluoroacetyl)hetarene-type ketones in the synthesis of trifluoromethyl-containing building blocks.[5,6] As a part of this program, we wish to report herein a very simple and practical one-step procedure for the preparation of new trifluoromethyl-substituted indole derivatives from 1*H*-indole and 2-trifluoroacetyl-1,3-heterazoles.

The starting 2-trifluoroacetyl-1,3-heterazoles **3–13** (Figure 2) were easily prepared by trifluoroacetylation of the corresponding 1,3-heterazoles with trifluoroacetic anhydride in the presence of triethylamine as described previously.[5] Recently, we have shown that the nucleophilic addition of compounds with an activated methylene group to the carbonyl group in ketones **3–13** provides the corresponding trifluoromethyl-substituted alcohols.[6a] We have extended this strategy to electron-rich heterocycles.



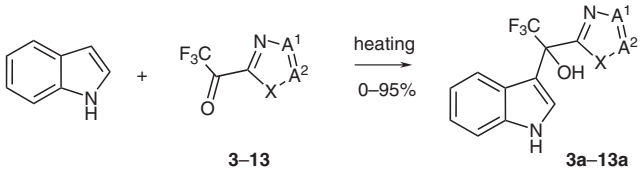
3 4 5
6 7 8
9 10 11
12 13

Figure 2 Trifluoromethyl ketones **3–13**

Unsubstituted 1*H*-indole was chosen as a model compound because it is known to react smoothly with both ketones **1** and **2**.[7] Indeed, substrates **3–12** showed excellent reactivity towards 1*H*-indole to provide trifluoromethyl-substituted alcohols **3a–12a** (Scheme 1 and Table 1, entries 1–10). As shown in Table 1, the yield of alcohols **3a–13a** depends strongly on the electron-withdrawing nature of the heterocyclic moiety in starting ketones **3–13**. For example, the addition of 1*H*-indole to ketones **3–8**, containing electron-deficient heterocyclic moieties, occurred smoothly on heating the reaction mixture at 60–80 °C in

SYNTHESIS 2010, No. 6, pp 0967–0970
Advanced online publication: 04.01.2010
DOI: 10.1055/s-0029-1219219; Art ID: Z22709SS

toluene for 30–60 minutes. The corresponding products **3a–8a** were obtained in 86–95% yield (entries 1–6).



Scheme 1 Synthesis of trifluoromethyl-substituted alcohols **3a–13a** from 1*H*-indole and the corresponding ketones **3–13**

Table 1 Reaction Conditions for the Synthesis of Trifluoromethyl-Substituted Alcohols **3a–13a**[a]

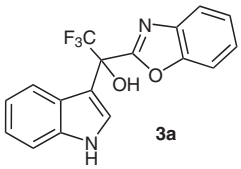
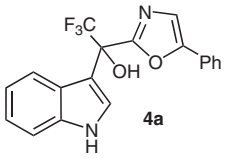
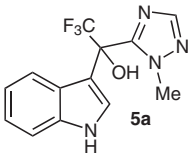
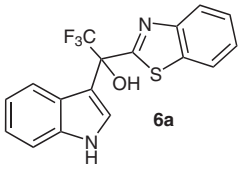
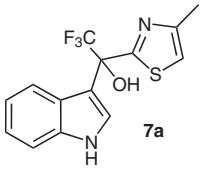
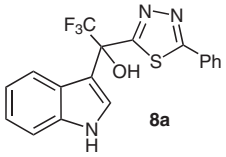
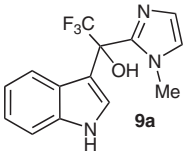
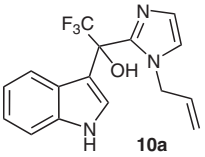
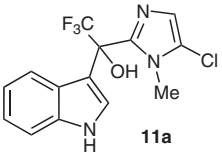
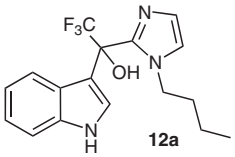
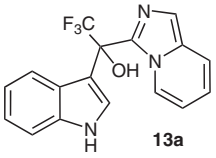
Entry	Ketone	Conditions	Product	Yield (%)
1	**3**	toluene, 60 °C, 0.5 h	 **3a**	95
2	**4**	toluene, 60 °C, 0.5 h	 **4a**	93
3	**5**	toluene, 80 °C, 0.5 h	 **5a**	87
4	**6**	toluene, 80 °C, 0.5 h	 **6a**	87
5	**7**	toluene, 80 °C, 1 h	 **7a**	90
6	**8**	toluene, 80 °C, 1 h	 **8a**	86
7	**9**	toluene, 100 °C, 1 h	 **9a**	85

Table 1 Reaction Conditions for the Synthesis of Trifluoromethyl-Substituted Alcohols **3a–13a**[a] (continued)

Entry	Ketone	Conditions	Product	Yield (%)
8	**10**	toluene, 100 °C, 1 h	 **10a**	57
9	**11**	toluene, 100 °C, 1 h	 **11a**	52
10	**12**	toluene, 100 °C, 2 h	 **12a**	49
11	**13**	neat, 160 °C, 2 h	 **13a**	0

[a] Compounds **4**, **6**, and **8** were used in the form of hydrates.

In contrast, the reaction of 1*H*-indole with ketones **9–12**, which are 1*H*-imidazole derivatives containing electron-donating alkyl groups, required harsher conditions (toluene, 100 °C, 1–2 h). The corresponding products **9a–12a** were isolated in 49–85% yield (Table 1, entries 7–10). The only exception to the above results was imidazo[1,5-*a*]pyridine derivative **13**, which did not react with 1*H*-indole even after heating the mixture of reactants without any solvent at 160 °C (entry 11). The behavior of compound **13**, in our opinion, can be explained by the poor electron-withdrawing nature of the imidazo[1,5-*a*]pyridine ring system.

It should be noted that the reaction of compounds **3–12** with 1*H*-indole does not require the use of an anhydrous solvent, as it could be efficiently performed in wet toluene, despite the starting ketones tending to react with water under these conditions.[5] Moreover, ketones **4**, **6**, and **8** form stable hydrates, which were used in the synthesis.

In summary, we have developed a very simple and efficient one-step procedure for the preparation of new trifluoromethyl-substituted alcohols **3a–12a** from 1*H*-indole and 2-trifluoroacetyl-1,3-heterazoles **3–12**. The yield of the target alcohols depends strongly on the electron-withdrawing nature of the 1,3-heterazole unit.

Ketones **3–13** were synthesized as previously reported.[5] Melting points were measured on a Thiele tube apparatus. The ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker Avance 500 spectrometer (at 499.9, 124.9, and 470.3 MHz, respectively). Chemical shifts

are reported in ppm downfield from TMS (^{1}H and ^{13}C NMR spectra) or $CFCl_3$ (^{19}F NMR spectra) as internal standards. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument by atmospheric pressure chemical ionization (APCI).

1-(1,3-Heterazol-2-yl)-Substituted 2,2,2-Trifluoro-1-(1*H*-indol-3-yl)ethanol; General Procedure

A mixture of the appropriate trifluoromethyl ketone (1 mmol), or its corresponding hydrate in the case of compounds **4**, **6**, and **8**, 1*H*-indole (1 mmol), and toluene (2 mL) was stirred under the conditions given in Table 1. The mixture was cooled to r.t., and the formed crystalline solid was collected by filtration. The product was washed with CCl_4 (0.5 mL) on the filter and then was recrystallized (*i*-PrOH). Reaction scale was 0.1–2.0 g of the starting trifluoromethyl ketone.

1-(1,3-Benzoxazol-2-yl)-2,2,2-trifluoro-1-(1*H*-indol-3-yl)ethanol (3a)

Colorless solid. Yield: 95%; mp 197–198 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 6.90 (dd, *J* = 8.4, 6.8 Hz, 1 H), 7.07 (dd, *J* = 8.0, 6.8 Hz, 1 H), 7.30 (d, *J* = 8.0 Hz, 1 H), 7.41 (d, *J* = 8.4 Hz, 1 H), 7.43–7.47 (m, 2 H), 7.50 (s, 1 H), 7.71–7.75 (m, 1 H), 7.88–7.92 (m, 1 H), 8.04 (s, 1 H), 11.43 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 74.71 (q, $^2J_{CF}$ = 31.0 Hz), 109.97, 111.67, 112.40, 119.91, 120.10, 121.10, 121.92, 125.03 (q, $^1J_{CF}$ = 286.7 Hz), 125.48, 125.49, 125.83, 126.64, 136.92, 140.43, 150.47, 162.75.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –76.46.

MS (APCI): *m*/*z* = 333 [M + 1].

2,2,2-Trifluoro-1-(1*H*-indol-3-yl)-1-(5-phenyl-1,3-oxazol-2-yl)ethanol (4a)

Colorless solid. Yield: 93%; mp 153–154 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 6.93 (t, *J* = 7.5 Hz, 1 H), 7.07 (t, *J* = 7.5 Hz, 1 H), 7.32–7.41 (m, 3 H), 7.42–7.47 (m, 3 H), 7.65 (d, *J* = 7.5 Hz, 2 H), 7.77 (s, 1 H), 7.83 (s, 1 H), 11.35 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 74.31 (q, $^2J_{CF}$ = 31.0 Hz), 110.46, 112.32, 119.79, 120.44, 121.86, 122.98, 124.58, 125.07 (q, $^1J_{CF}$ = 286.7 Hz), 125.60, 125.79, 127.52, 129.37, 129.62, 136.84, 151.72, 160.24.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –76.70.

MS (APCI): *m*/*z* = 359 [M + 1].

2,2,2-Trifluoro-1-(1*H*-indol-3-yl)-1-(1-methyl-1*H*-1,2,4-triazol-5-yl)ethanol (5a)

Colorless solid. Yield: 87%; mp 213–215 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.51 (s, 3 H), 6.86 (dd, *J* = 7.5, 7.0 Hz, 1 H), 6.91 (d, *J* = 7.5 Hz, 1 H), 7.05 (dd, *J* = 8.0, 7.0 Hz, 1 H), 7.38 (d, *J* = 8.0 Hz, 1 H), 7.43 (d, *J* = 2.5 Hz, 1 H), 7.74 (s, 1 H), 8.01 (s, 1 H), 11.40 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 37.29, 73.50 (q, $^2J_{CF}$ = 31.0 Hz), 110.06, 112.39, 119.49, 119.92, 121.89, 125.13, 125.26 (q, $^1J_{CF}$ = 286.7 Hz), 125.80, 136.90, 149.51, 152.39.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –76.74.

MS (APCI): *m*/*z* = 297 [M + 1].

1-(1,3-Benzothiazol-2-yl)-2,2,2-trifluoro-1-(1*H*-indol-3-yl)ethanol (6a)

Colorless solid. Yield: 87%; mp 159–160 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 6.91 (t, *J* = 7.5 Hz, 1 H), 7.07 (t, *J* = 7.5 Hz, 1 H), 7.40 (d, *J* = 7.5 Hz, 1 H), 7.43–7.54 (m, 3 H), 7.56 (s, 1 H), 8.02 (d, *J* = 7.5 Hz, 1 H), 8.14 (d, *J* = 7.5 Hz, 1 H), 8.23 (s, 1 H), 11.36 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 77.05 (q, $^2J_{CF}$ = 30.2 Hz), 111.11, 112.32, 119.77, 120.91, 122.00, 122.77, 123.73, 125.27 (q, $^1J_{CF}$ = 286.7 Hz), 125.40, 125.75, 126.07, 126.76, 135.32, 136.89, 153.45, 172.88.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –76.44.

MS (APCI): *m*/*z* = 349 [M + 1].

2,2,2-Trifluoro-1-(1*H*-indol-3-yl)-1-(4-methyl-1,3-thiazol-2-yl)ethanol (7a)

Colorless solid. Yield: 90%; mp 131–133 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.35 (s, 3 H), 6.94 (dd, *J* = 8.0, 6.8 Hz, 1 H), 7.08 (dd, *J* = 8.0, 6.8 Hz, 1 H), 7.33 (s, 1 H), 7.39 (d, *J* = 8.0 Hz, 1 H), 7.46 (d, *J* = 8.0 Hz, 1 H), 7.50 (s, 1 H), 7.90 (s, 1 H), 11.30 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 17.46, 76.72 (q, $^2J_{CF}$ = 29.7 Hz), 111.78, 112.17, 116.20, 119.58, 121.27, 121.85, 125.32 (q, $^1J_{CF}$ = 286.7 Hz), 125.35, 125.93, 136.90, 152.80, 170.46.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –76.86.

MS (APCI): *m*/*z* = 313 [M + 1].

2,2,2-Trifluoro-1-(1*H*-indol-3-yl)-1-(5-phenyl-1,3,4-thiadiazol-2-yl)ethanol (8a)

Colorless solid. Yield: 86%; mp 218–219 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 6.98 (dd, *J* = 8.0, 7.0 Hz, 1 H), 7.11 (dd, *J* = 8.0, 7.0 Hz, 1 H), 7.43 (d, *J* = 8.0 Hz, 1 H), 7.49 (d, *J* = 8.0 Hz, 1 H), 7.55–7.65 (m, 4 H), 8.01 (d, *J* = 7.0 Hz, 2 H), 8.43 (s, 1 H), 11.44 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 75.95 (q, $^2J_{CF}$ = 31.0 Hz), 110.77, 112.42, 119.97, 120.81, 122.13, 125.07 (q, $^1J_{CF}$ = 287.6 Hz), 125.57, 125.67, 128.22, 129.78, 129.96, 132.06, 136.99, 169.91, 172.53.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –76.95.

MS (APCI): *m*/*z* = 376 [M + 1].

2,2,2-Trifluoro-1-(1*H*-indol-3-yl)-1-(1-methyl-1*H*-imidazol-2-yl)ethanol (9a)

Colorless solid. Yield: 85%; mp 210–212 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.21 (s, 3 H), 6.73 (d, *J* = 8.0 Hz, 1 H), 6.81 (dd, *J* = 8.0, 6.8 Hz, 1 H), 6.95 (s, 1 H), 7.03 (dd, *J* = 8.0, 6.8 Hz, 1 H), 7.06 (s, 1 H), 7.29 (s, 1 H), 7.37 (d, *J* = 8.0 Hz, 1 H), 7.40 (s, 1 H), 11.30 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 34.15, 74.00 (q, $^2J_{CF}$ = 29.8 Hz), 111.54, 112.18, 119.63, 119.72, 121.66, 124.13, 125.55, 125.60, 125.64 (q, $^1J_{CF}$ = 286.7 Hz), 125.80, 136.78, 144.18.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –75.81.

MS (APCI): *m*/*z* = 296 [M + 1].

1-(1-Allyl-1*H*-imidazol-2-yl)-2,2,2-trifluoro-1-(1*H*-indol-3-yl)ethanol (10a)

Colorless solid. Yield: 57%; mp 155–156 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 4.22–4.40 (m, 2 H), 4.82–4.94 (m, 2 H), 5.26–5.38 (m, 1 H), 6.75 (d, *J* = 8.0 Hz, 1 H), 6.81 (dd, *J* = 8.0, 7.0 Hz, 1 H), 6.99 (s, 1 H), 7.02 (dd, *J* = 8.0, 7.0 Hz, 1 H), 7.06 (s, 1 H), 7.35 (d, *J* = 8.0 Hz, 1 H), 7.38–7.42 (m, 2 H), 11.29 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 49.06, 74.11 (q, $^2J_{CF}$ = 29.8 Hz), 112.03, 112.12, 118.34, 119.64, 119.80, 121.63, 122.08, 125.33, 125.58 (q, $^1J_{CF}$ = 286.7 Hz), 125.72, 126.51, 133.88, 136.78, 144.09.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –75.93.

MS (APCI): m/z = 322 [M + 1].

1-(5-Chloro-1-methyl-1*H*-imidazol-2-yl)-2,2,2-trifluoro-1-(1*H*-indol-3-yl)ethanol (11a)

Colorless solid. Yield: 52%; mp 173 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.16 (s, 3 H), 6.82–6.88 (m, 2 H), 7.01–7.07 (m, 1 H), 7.10 (s, 1 H), 7.38 (d, J = 8.5 Hz, 1 H), 7.42 (d, J = 2.5 Hz, 1 H), 7.49 (s, 1 H), 11.37 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 31.62, 74.24 (q, $^2J_{CF}$ = 29.8 Hz), 110.79, 112.29, 119.23, 119.42, 119.85, 121.74, 123.17, 125.34 (q, $^1J_{CF}$ = 286.7 Hz), 125.37, 125.76, 136.82, 144.50.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –76.00.

MS (APCI): m/z = 330 [M + 1].

1-(1-Butyl-1*H*-imidazol-2-yl)-2,2,2-trifluoro-1-(1*H*-indol-3-yl)ethanol (12a)

Colorless solid. Yield: 49%; mp 168–169 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.51 (t, J = 6.5 Hz, 3 H), 0.86–0.89 (m, 3 H), 1.28–1.31 (m, 1 H), 3.55–3.58 (m, 1 H), 3.80–3.83 (m, 1 H), 6.76 (d, J = 8.0 Hz, 1 H), 6.81 (dd, J = 8.0, 7.0 Hz, 1 H), 6.98 (s, 1 H), 7.02 (dd, J = 8.0, 7.0 Hz, 1 H), 7.17 (s, 1 H), 7.33 (s, 1 H), 7.37 (d, J = 8.0 Hz, 1 H), 7.44 (s, 1 H), 11.33 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 13.64, 19.59, 31.99, 46.09, 74.11 (q, $^2J_{CF}$ = 29.3 Hz), 112.02, 112.17, 119.56, 119.75, 121.56, 122.20, 125.18, 125.63 (q, $^1J_{CF}$ = 286.7 Hz), 125.78, 126.18, 136.75, 144.04.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –75.96.

MS (APCI): m/z = 338 [M + 1].

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