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Trifluoroacetic Anhydride Mediated Oxidative Functionalization of Some 2-Dimethylaminoethyl-Substituted Indoles

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Summary. 2′-Dimethylamino-1′-trifluoroacetyl-2-vinylindole derivatives were prepared by trifluoroacetic anhydride assisted oxidation.

Keywords. β-Enamino trifluoromethylketone; Heterocycles; Oxidations; Trifluoroacetic anhydride; 2-Vinylindole.

Introduction

Trifluoromethyl substituted heterocycles have received great attention over the past decade due to their enhanced reactivity and promising biological activities [1]. With regard to these properties, we have published an efficient method for the preparation of trifluoromethyl-containing nitrogen heterocycles using N,N-diethylaminomethylene hexafluoroacetylacetone (*DAMFA*) as fluorine source some years ago [2]. The same β-enamino-trifluoromethylketone moiety was introduced by trifluoroacetic anhydride (*TFAA*) assisted oxidation in *Aspidosperma* series [3].

In continuation of our interest in the chemistry of 2-vinylindoles we report herein a trifluoroacetic anhydride (*TFAA*) mediated oxidative functionalization of the dimethylaminoethyl side chain of some 1,2-disubstituted indole derivatives, providing new functionalized 2-vinylindoles.

Results and Discussion

2-Dimethylaminoethyl indoles (**1a**–**d**) were prepared by classical reactions starting from tetrahydro-γ-carboline (**2**). Thus, cyanide cleavage of the quaternary ammonium salt of **2** led to nitrile **1a** [4], whose methanolysis afforded the corresponding methyl ester **1b** [5]. Hydride reduction of the nitrile followed by

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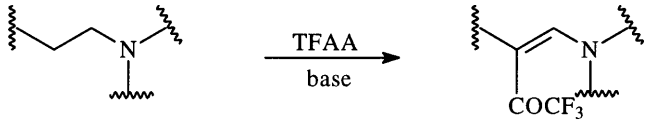
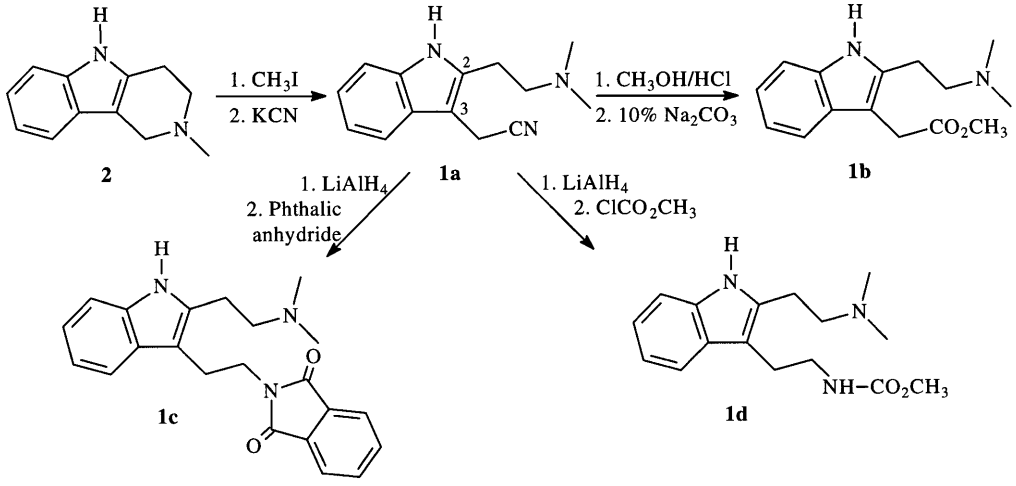


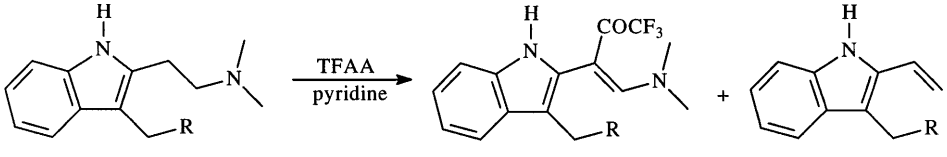
Fig. 1. Oxidative functionalization by *TFAA*



Scheme 1

primary amine protection allowed the preparation of phthalimido [4] and urethane derivatives **1c** and **1d**.

Treatment of nitrile **1a** with a large excess (5 equiv.) of *TFAA* in pyridine at 50°C for 2–5 days afforded a complex mixture from which enaminotrifluoromethylketone **3a**, the known 2-vinylindole **4a** [4], and a great amount (30–40%) of unreacted starting material **1a** could be isolated by chromatography (Scheme 2). The structure of **3a** was supported spectroscopically. In the ^{1}H NMR spectrum, the non-equivalent N-methyl singlets at $\delta = 2.48$ and 3.18 ppm and the olefinic proton at $\delta = 8.02$ ppm were in accordance with the enaminone moiety. Incorporation of the trifluoroacetyl group was evidenced in ^{13}C NMR by the presence of two sets of quartets at $\delta = 117.8$ ($^{1}J_{C-F} = 285$ Hz) and 176.3 ($^{2}J_{C-F} = 37$ Hz) ppm, attributed to the CF_3 and CO functions, respectively.



Scheme 2

Table 1. Trifluoroacetic anhydride (*TFAA*) assisted oxidative functionalization of 2-dimethylaminoethylindoles

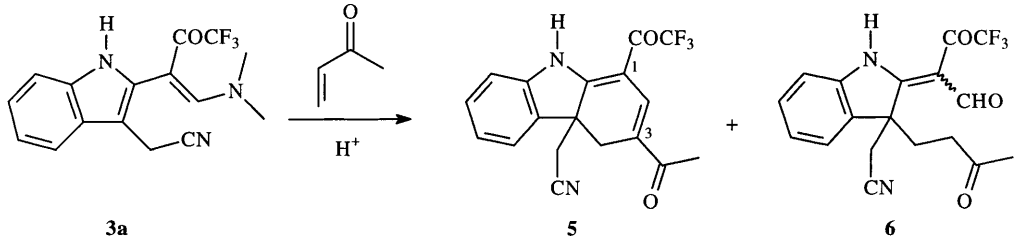
Entry	Starting material	Conditions	*TFAA* (equiv.)	**3** (%)	**4** (%)	Recovered **1** (%)
1	**1a**	50°C, 48 h	5	22	3	42
2	**1a**	50°C, 120 h	5	19	5	31
3	**1a**	50°C, 96 h	5 + 5[a]	28	21	43
4	**1a**	40–50°C, microwave, 1 h	5	39	11	11
5	**1a**	40–50°C, microwave, *DMAP* (cat), 30 min	5	42	8	7
6	**1a**	40–50°C, microwave, *DMAP* (cat), Al_2O_3, 10 min	5	45	5	8
7	**1b**	60°C, 48 h	5	41	–	42
8	**1c**	70°C, 72 h	5	40	2	33
9	**1d**	70°C, 48 h	5	32[b]	–	38

[a] With 48 h interval; [b] $NHCO_2CH_3$ group was replaced by $NHCOCF_3$

As shown in Table 1, detailed experiments revealed that reactions activated by conventional heating led to functionalized enaminones **3a**–**d** with relatively homogenous yields (entries 7–9) except for **3a**. In this series, two-fold addition of *TFAA* allowed to enhance slightly the yield of **3a** and markedly that of **4a** (entry 3), but the quantity of recovered starting material remained high. It has to be noted that under conventional heating conditions urethane **1d** was transformed into N-trifluoracetamide **3d**.

However, by microwave assisted activation we realized acceptable chemical yields. Thus, treatment of nitrile **1a** in a mixture of *TFAA* and pyridine gave rise to **3a** in 39% yield (entry 4). Slight improvements were achieved by using 4-dimethylaminopyridine (*DMAP*) as acyl group transfer catalyst [6] (entry 5). Finally, irradiation of **1a** in the presence of *TFAA*, pyridine, and *DMAP* adsorbed on neutral alumina support afforded **3a** in 45% yield in a cleaner and shorter reaction (entry 6). For the formation of enamino-trifluoromethylketones (**3a**–**d**), *Schreiber* has proposed a plausible mechanism *via* hydrogen transfer followed by enamine acylation [7], whereas 2-vinylindoles (**4a**,**c**) could result from a *Hofmann*-like degradation of the primarily formed acylammonium salts [8].

β-Enamino trifluoromethylketones proved to be useful synthetic intermediates for the preparation of trifluoromethyl-substituted heterocycles [9]. Indole-substituted β-trifluoroacetyl enamines like **3a**–**d** may be considered as highly



3a **5** **6**

Scheme 3

functionalized 2-vinylindoles, reactive species for [4 + 2]-cyclizations toward carbazole derivatives. In order to test their reactivity, 3-cyanomethyl derivative **3a** was reacted with donor and acceptor type dienophiles.

Treatment of **3a** with methyl vinyl ether led to a very complex unexploitable reaction mixture; however, reaction with methyl vinyl ketone afforded the tricyclic compound **5** as main product (67%). The dihydrocarbazolic nature of **5** was suggested by characteristic UV/Vis absorptions (237, 251, 259, 329, 432 nm), by the carbonyl bands in the IR spectrum (1670, 1645 cm^{-1}), and by the intense mass fragments at $m/z = 306$, 264 and 167 resulting from the successive loss of ring substituents. In the ^1H NMR spectrum, a one-proton singlet at $\delta = 7.51$ ppm could be attributed the olefinic proton of ring C. Further NMR data, including results from HMBC and HMQC experiments, were in full agreement with the proposed tricyclic structure of **5**. For the formation of **5**, both a *Diels-Alder* reaction and a *Michael*-type process followed by cyclization could be envisioned. However, the latter was supported by the isolation and characterisation of the *Michael*-type minor intermediate **6** (12%) which could be slowly transformed into **5** under the same reaction conditions. In conclusion, highly functionalized indolyl β-enamino trifluoromethylketone derivatives **3** were prepared by means of trifluoroacetic anhydride assisted oxidation. The evaluation of their synthetic applicability for the preparation of different trifluoromethyl containing heterocycles is in progress.

Experimental

Microwave irradiations were carried out with a Normalab Analis Normatron 112 oven. Melting points were determined on a Reichert Thermovar hot-stage apparatus and are uncorrected. UV/Vis spectra were recorded in MeOH solution on a UNICAM 8700 UV/Vis spectrophotometer. IR spectra were measured with a Bomen FTIR instrument. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were acquired on a Bruker AC 300 spectrometer using *TMS* as internal standard. Mass spectra were recorded with a VG Autospec apparatus. Reactions were monitored using Merck TLC aluminum sheets (Kieselgel 60 F_{254}). The results of elemental analyses were found to be in satisfactory agreement with the calculated values.

(2-(1-Dimethylaminomethylene-3,3,3-trifluoro-2-oxo-propyl)-1H-indol-3-yl)-acetonitrile (**3a**; $C_{16}H_{14}N_3OF_3$); *general procedure*

Conventional heating: To a stirred solution of 2.00 g **1a** (8.81 mmol) in 15 cm^3 pyridine, 18.50 g trifluoroacetic anhydride (88.10 mmol) were added dropwise within 15 min. The mixture was stirred at 50°C for 96 h. After evaporation to dryness, the residue was dissolved in 20 cm^3 H_2O, rendered alkaline with 10% Na_2CO_3 to *pH* 9, and extracted with 3 × 30 cm^3 CH_2Cl_2. The organic layers were dried (Na_2SO_4), filtered, evaporated, and purified by flash chromatography (eluant: CH_2Cl_2: MeOH = 10:1) to afford 0.80 g (28%) **3a**, 0.35 g (21%) (2-vinyl-1*H*-indol-3-yl)-acetonitrile (**4a**, [4]), and some recovered starting material **1a** (0.85 g, 43%).

Microwave irradiation: A mixture of 0.33 g **1a** (1.45 mmol) in 2.5 cm^3 pyridine, 1.58 g trifluoroacetic anhydride (7.50 mmol), 0.003 g 4-dimethylaminopyridine (0.025 mmol), and 1.5 g neutral aluminum oxide (70–230 mesh, Merck) was heated by microwave irradiation at 50°C for 10 min. The aluminum oxide was filtered and washed with CH_2Cl_2. After evaporation of the pyridine, the filtrate was rendered alkaline with 10% Na_2CO_3 and extracted with 3 × 20 cm^3 CH_2Cl_2. The organic layers were dried (Na_2SO_4), filtered, evaporated, and purified by flash chromatography

(eluant: CH_2Cl_2:MeOH = 10:1) to afford 0.20 g (43%) **3a**, 0.01 g (5%) **4a**, and some recovered starting material **1a** (0.03 g, 8%).

3a: White-grey powder; m.p.: 174–175°C; UV/Vis (CH_3OH): $\lambda_{max} = 218$, 284, 291, 321, 326 nm; IR (KBr): $\nu = 3333$, 2245, 1659, 1578 cm^{-1}; ^1H NMR ($CDCl_3$, 300 Hz): $\delta = 2.47$ (3H, s), 3.19 (3H, s), 3.61 (1H, AB system, $J = 17.7$ Hz), 3.74 (1H, AB system, $J = 17.7$ Hz), 7.20 (1H, t, $J = 8.0$ Hz), 7.25 (1H, t, $J = 8.0$ Hz), 7.40 (1H, d, $J = 8.0$ Hz), 7.64 (1H, d, $J = 8.0$ Hz), 8.00 (1H, s), 8.71 (1H, br) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 13.3$, 38.0, 48.3, 92.4, 106.2, 111.4, 112.8, 116.0, 117.7, 118.3, 119.9, 120.4, 122.9, 123.2, 126.3, 127.9, 135.7, 157.2, 176.5 ppm; MS: m/z (%) = 321 (M^+, 35), 281 (12), 276 (20), 183 (100), 154 (39); HREIMS: calcd. 321.108897, found 321.109047.

(2-(1-Dimethylaminomethylene-3,3,3-trifluoro-2-oxo-propyl)-1H-indol-3-yl)-acetic acid methyl ester (**3b**; $C_{17}H_{17}N_2O_3F_3$)

White-grey powder; m.p.: 69–71°C; UV/Vis (CH_3OH): $\lambda_{max} = 219$, 285, 292, 319 nm; IR (KBr): $\nu = 3405$, 1734, 1672, 1576 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 2.49$ (3H, s), 3.14 (3H, s), 3.58 (1H, AB system, $J = 14.2$ Hz), 3.60 (1H, AB system, $J = 14.2$ Hz), 3.65 (3H, s), 7.13 (1H, t, $J = 8.0$ Hz), 7.21 (1H, t, $J = 8.0$ Hz), 7.35 (1H, d, $J = 8.0$ Hz), 7.58 (1H, d, $J = 8.0$ Hz), 8.00 (1H, s), 8.41 (1H, br) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 30.8$, 38.0, 48.2, 51.7, 91.9, 111.0, 112.5, 113.5, 116.0, 119.2, 119.8, 120.0, 122.5, 123.4, 126.5, 127.5, 135.7, 157.0, 172.3, 176.6 ppm; MS: m/z (%) = 354 (M^+, 100), 309 (40), 295 (62), 279 (83), 183 (57), 154 (54); HREIMS: calcd. 354.129820, found 354.131003.

2-(2-(2-(1-Dimethylaminomethylene-3,3,3-trifluoro-2-oxo-propyl)-1H-indol-3-yl)-ethyl)-isoindole-1,3-dione (**3c**; $C_{24}H_{20}N_3O_3F_3$)

White-grey powder; m.p.: 127–129°C; UV/Vis (CH_3OH): $\lambda_{max} = 219$, 287, 294, 322 nm; IR (KBr): $\nu = 3383$, 1771, 1709, 1670, 1579 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 2.47$ (3H, s), 2.98 (2H, m), 3.21 (3H, s), 3.84 (1H, m), 3.98 (1H, m), 7.15 (1H, t, $J = 8.0$ Hz), 7.20 (1H, t, $J = 8.0$ Hz), 7.35 (1H, d, $J = 8.0$ Hz), 7.70 (2H, m), 7.81 (1H, d, $J = 8.0$ Hz), 7.83 (2H, m), 8.00 (1H, s), 8.30 (1H, br) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 24.4$, 37.4, 38.2, 48.0, 94.3, 111.1, 112.2, 113.9, 116.1, 119.1, 119.5, 119.9, 122.2, 123.1, 123.8, 126.9, 127.4, 132.2, 133.8, 136.0, 156.7, 168.2, 177.5 ppm; MS: m/z (%) = 455 (M^+, 50), 295 (100), 279 (43), 263 (22), 183 (16), 160 (39), 154 (30); HREIMS: calcd. 455.149394, found 455.149810.

2-(2-(2-Vinyl-1H-indol-3-yl)-ethyl)-isoindole-1,3-dione (**4c**; $C_{20}H_{16}N_2O_2$)

The physical data of **4c** complied with those given in Ref. [4].

N-(2-(2-(1-Dimethylaminomethylene-3,3,3-trifluoro-2-oxo-propyl)-1H-indol-3-yl)-ethyl)-trifluoro-acetamide (**3d**; $C_{18}H_{17}N_3O_2F_6$)

White-grey powder; m.p.: 79–81°C; UV/Vis (CH_3OH): $\lambda_{max} = 204$, 220, 288, 294, 315, 326 nm; IR (KBr): $\nu = 3418$, 3397, 1705, 1653, 1576 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 2.38$ (3H, s), 2.73 (1H, m), 3.01 (1H, m), 3.12 (3H, s), 3.65 (2H, m), 7.11 (1H, t, $J = 8.0$ Hz), 7.15 (1H, br), 7.18 (1H, t, $J = 8.0$ Hz), 7.30 (1H, d, $J = 8.0$ Hz), 7.57 (1H, d, $J = 8.0$ Hz), 7.82 (1H, s), 8.51 (1H, br) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 24.0$, 37.8, 39.5, 48.2, 92.4, 110.5, 111.3, 112.4, 113.2, 113.6, 116.2, 117.7, 118.6, 119.7, 120.1, 121.7, 122.5, 123.9, 127.0, 127.2, 136.0, 156.6, 157.2, 177.7 ppm; MS: m/z (%) = 421 (M^+, 78), 295 (100), 279 (60), 263 (23), 202 (33), 183 (20), 154 (34); HREIMS: calcd. 421.121584, found 421.121503.

(3-Acetyl-1-trifluoroacetyl-4,9-dihydro-carbazol-4a-yl)-acetonitrile (**5**; $C_{18}H_{13}N_2O_2F_3$) *and (3-(3-Oxo-butyl)-2-(3,3,3-trifluoro-1-formyl-2-oxo-propylidene)-2,3-dihydro-1H-indol-3-yl)-acetonitrile* (**6**; $C_{18}H_{15}N_2O_3F_3$)

A mixture of 0.20 g **3a** (0.62 mmol) in 20 cm^3 CH_2Cl_2, 0.43 g methyl vinyl ketone (6.20 mmol), and 2.98 g trifluoroacetic acid (26.14 mmol) was stirred at room temperature for 100 h. The reaction mixture was rendered alkaline with 10% Na_2CO_3 to *pH* 9 and extracted with 3×15 cm^3 CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered, evaporated, and purified by flash chromatography (eluant: hexane:EtOAc = 10:1 → 1:1) to afford 0.14 g (67%) **5** and 0.03 g (12%) **6**.

5: Yellow powder; m.p.: 155–157°C; UV/Vis (CH_3OH): $\lambda_{max} = 194$, 203, 237, 251, 259, 329, 432 nm; IR (KBr): $\nu = 3279$, 2251, 1670, 1645, 1593, 1547, 1481 cm^{-1}; ^{1}H NMR (*DMSO*-d_6, 300 MHz): $\delta = 2.38$ (3H, s), 2.41 (1H, AB system, $J = 17.3$ Hz), 2.98 (1H, AB system, $J = 16.7$ Hz), 3.11 (1H, AB system, $J = 16.7$ Hz), 3.48 (1H, AB system, $J = 17.3$ Hz), 7.29 (1H, t, $J = 7.5$ Hz), 7.45 (1H, t, $J = 7.5$ Hz), 7.51 (1H, s), 7.60 (1H, d, $J = 7.5$ Hz), 7.68 (1H, d, $J = 7.5$ Hz), 12.75 (1H, br) ppm; ^{13}C NMR (*DMSO*-d_6, 75 MHz): $\delta = 24.4$, 25.2, 26.6, 50.0, 96.0, 111.6, 114.4, 115.5, 116.8, 119.4, 123.4, 123.5, 123.8, 125.1, 129.8, 132.8, 133.5, 144.1, 171.1, 172.6, 196.2 ppm; MS: m/z (%) = 346 (M^+, 58), 306 (33), 290 (18), 264 (100), 194 (25), 167 (40); HREIMS: calcd. 364.092913, found 346.094124.

6: White powder; m.p.: 225–227°C; UV (CH_3OH): $\lambda_{max} = 202$, 246, 253, 273, 366 nm; IR (KBr): $\nu = 3131$, 2258, 1713, 1674, 1630, 1613, 1516, 1474 cm^{-1}; ^{1}H NMR (*DMSO*-d_6, 300 MHz): $\delta = 1.65$ (1H, m), 1.89 (3H, s), 2.05 (1H, m), 2.30 (1H, m), 2.87 (1H, m), 3.68 (1H, AB system, $J =$ 17.0 Hz), 3.98 (1H, AB system, $J = 17.0$ Hz), 7.39 (1H, t, $J = 7.5$ Hz), 7.46 (1H, t, $J = 7.5$ Hz), 7.66 (1H, d, $J = 7.5$ Hz), 7.80 (1H, d, $J = 7.5$ Hz), 9.81 (1H, s), 13.88 (1H, br) ppm; ^{13}C NMR (*DMSO*-d_6, 75 MHz): $\delta = 23.6$, 27.7, 29.7, 37.5, 57.7, 105.5, 111.6, 115.2, 115.4, 117.0, 119.4, 123.0, 123.2, 127.0, 129.8, 134.6, 140.9, 175.1, 176.6, 186.5, 206.6 ppm; MS: m/z (%) = 364 (M^+, 72), 307 (100), 278 (37), 266 (62), 209 (17), 195 (38), 168 (68), 140 (58), 128 (27), 115 (38); HREIMS: calcd. 364.103477, found 364.103073.

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