A convenient synthesis of 4(5)-(2-hydroxyaroyl)-5(4)-trifluoromethyl-1,2,3-triazoles from 2-trifluoromethylchromones and chromen-4-imines

Vyacheslav Ya. Sosnovskikh* and Boris I. Usachev

Department of Chemistry, A. M. Gor'ky Urals State University, 620083 Ekaterinburg, Russian Federation.
Fax: +7 3432 61 5978; e-mail: Vyacheslav.Sosnovskikh@usu.ru

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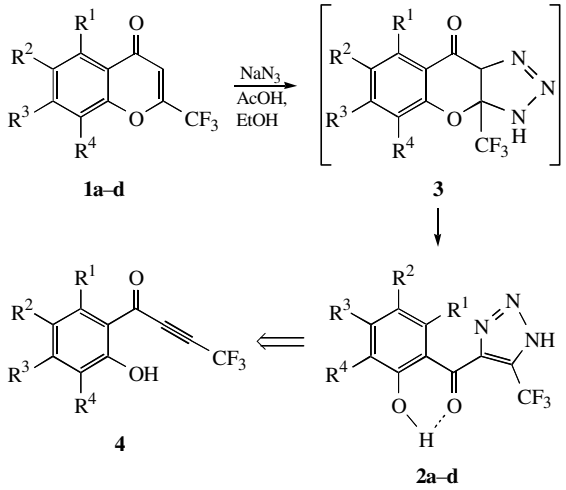
The reactions of 2-trifluoromethylchromones and 2-trifluoromethyl-4*H*-chromen-4-imines with sodium azide in the presence of acetic acid give the ketone and imine derivatives of 5(4)-trifluoromethyl-1,2,3-triazole in high yields.

Vicinal triazoles belong to well-studied heterocyclic systems formed by the reactions of organic and inorganic azides with activated acetylenes[1–4] and alkenes.[5–8] However, data on 1,2,3-triazoles with CF_3 groups are scanty, although CF_3-containing heterocycles are widely used in medicine and agriculture.[9] They are primarily prepared by the cycloaddition reactions of organic azides to CF_3-containing acetylenes[10–13] and by the oxidation of polyfluorinated aliphatic α-diketone bishydrazones.[14]

To continue our studies[15–18] on the chemical properties of 2-trifluoromethylchromones, we examined the reactions of chromones **1a–d** with sodium azide. We found that this is a simple and effective method for the synthesis of previously unknown salicyloyltriazoles **2a–d**.† It is most likely that the reaction occurs *via* intermediate **3**, which results from 1,3-dipolar cycloaddition or the initial attack of the azide anion on the C(2) atom followed by cyclization to **3**. Ring opening in intermediate **3** results in aryl triazolyl ketones **2** in 50–86% yields; thus, chromones **1** can be considered as synthetic equivalents of inaccessible trifluoropropynyl ketones **4**.

The reaction of chromones **1** with NaN_3 occurred in AcOH–EtOH at 80 °C within 4–10 h. However, it was found that this reaction is typical of only 2-trifluoromethylchromones, and it did not take place on the replacement of CF_3 by H, CF_2H, $(CF_2)_2H$ and CCl_3 groups, as well as with 3-chloro-2-trifluoromethylchromone. Moreover, in the absence of an electron-acceptor substituent at the 6-position of the chromone system, the reaction was slow so that 2-trifluoromethylchromone remained unconverted after contact with NaN_3 under the above conditions for 10 h.

We found that the replacement of C=O with the C=N–R group enhanced the reactivity of the double bond of a pyrone ring towards sodium azide. Thus, chromen-4-imines **5**, which were synthesised by the condensation of the Schiff bases of 2-hydroxy- and 2-hydroxy-5-methylacetophenones with CF_3CO_2Et followed by the cyclisation of resulting aminoenones **6** to cations **5′** under the action of HCl and the treatment of the latter with an aqueous ammonia solution,[19] readily react with NaN_3 in the presence of AcOH to form aryl triazolyl ketone imines **7**.‡ This result can be explained by the fact that compounds **5**, which are



1a–d **3** **4** **2a–d**

a $R^1 = R^3 = R^4 = H$, $R^2 = NO_2$
b $R^1 = R^3 = R^4 = H$, $R^2 = Cl$
c $R^1 = R^3 = H$, $R^2 = R^4 = Br$
d $R^1 = R^3 = Me$, $R^2 = R^4 = NO_2$

Scheme 1

† *General preparation procedure for triazoles* **2**. A mixture of chromone **1** (1.0 mmol) and NaN_3 (0.10 g, 1.5 mmol) in 2 ml of AcOH–EtOH (1:1) was heated at 80 °C for 4 h for **1a**,**c** or 10 h for **1b**,**d**. Next, the reaction mixture was mixed with 10 ml of water; the product was filtered off, washed with water, dried and recrystallised.

4(5)-(2-Hydroxy-5-nitrobenzoyl)-5(4)-trifluoromethyl-1,2,3-triazole **2a**: yield 86%, mp 177–178 °C (CCl_4). ^{1}H NMR (400 MHz, [$^2H_6$]DMSO) δ: 7.16 [d, 1H, H(3), ^oJ 9.1 Hz], 8.35 [dd, 1H, H(4), ^oJ 9.1 Hz, ^mJ 2.9 Hz], 8.52 [d, 1H, H(6), ^mJ 2.9 Hz], 11.9 (br. s, 1H, NH or OH). IR (Vaseline oil, ν/cm^{-1}): 3270, 1680, 1640, 1615, 1570, 1515. Found (%): C, 39.65; H, 1.79; N, 18.58. Calc. for $C_{10}H_5F_3N_4O_4$ (%): C, 39.75; H, 1.67; N, 18.54.

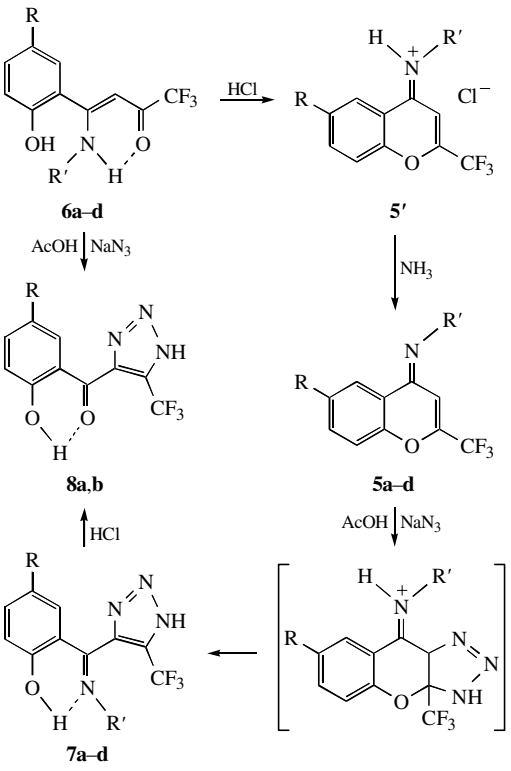
4(5)-(5-Chloro-2-hydroxybenzoyl)-5(4)-trifluoromethyl-1,2,3-triazole **2b**: yield 68%, mp 148–149 °C (hexane–toluene). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.05 [d, 1H, H(3), ^oJ 9.0 Hz], 7.52 [dd, 1H, H(4), ^oJ 9.0 Hz, ^mJ 2.6 Hz], 8.27 [d, 1H, H(6), ^mJ 2.6 Hz], 11.80 (s, 1H, NH or OH). IR (Vaseline oil, ν/cm^{-1}): 3350, 1625, 1605, 1560, 1525, 1495. Found (%): C, 41.14; H, 1.72; N, 14.68. Calc. for $C_{10}H_5ClF_3N_3O_2$ (%): C, 41.19; H, 1.73; N, 14.41.

4(5)-(3,5-Dibromo-2-hydroxybenzoyl)-5(4)-trifluoromethyl-1,2,3-triazole **2c**: yield 50%, mp 175–176 °C (hexane–toluene). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.96 [d, 1H, H(4), ^mJ 2.3 Hz], 8.43 [d, 1H, H(6), ^mJ 2.3 Hz], 12.44 (s, 1H, NH or OH). IR (Vaseline oil, ν/cm^{-1}): 3190, 1635, 1585. Found (%): C, 29.25; H, 1.18; N, 10.41. Calc. for $C_{10}H_4Br_2F_3N_3O_2$ (%): C, 28.94; H, 0.97; N, 10.13.

4(5)-(4,6-Dimethyl-3,5-dinitro-2-hydroxybenzoyl)-5(4)-trifluoromethyl-1,2,3-triazole **2d**: yield 66%, mp 160–161 °C (hexane–CCl_4). ^{1}H NMR (400 MHz, [$^2H_6$]DMSO) δ: 2.06 (s, 3H, Me), 2.22 (s, 3H, Me), 6.2 (br. s, 2H, OH, NH). IR (Vaseline oil, ν/cm^{-1}): 3280, 1695, 1590, 1535. Found (%): C, 38.43; H, 2.06; N, 18.61. Calc. for $C_{12}H_8F_3N_5O_6$ (%): C, 38.41; H, 2.15; N, 18.67.

‡ *2-[Benzylimino-(1,2,3-triazol-4-yl)methyl]phenol* **7a** was prepared from compound **5a** according to a procedure analogous to that for **2**; however, the heating was performed for 10 min. Yield 57%, mp 146–147 °C (ethanol–H_2O, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.50 (s, 2H, CH_2), 6.64 [dd, 1H, H(6), ^oJ 8.0 Hz, ^mJ 1.6 Hz], 6.74 [ddd, 1H, H(5), ^oJ 8.0, 7.3 Hz, ^mJ 1.1 Hz], 7.06 [dd, 1H, H(3), ^oJ 8.4 Hz, ^mJ 1.0 Hz], 7.24–7.33 (m, 5H, Ph), 7.35 [ddd, 1H, H(4), ^oJ 8.4, 7.3 Hz, ^mJ 1.7 Hz], 11.3 (br. s, 1H, NH). ^{1}H NMR (400 MHz, $CDCl_3$ + CF_3CO_2H) δ: 4.72 (s, 2H, CH_2), 6.81 [dd, 1H, H(6), ^oJ 8.3 Hz, ^mJ 1.5 Hz], 6.96 [t, 1H, H(5), ^oJ 8.1 Hz], 7.31 [d, 1H, H(3), ^oJ 8.5 Hz], 7.15–7.17 [m, 2H, H(3′), H(5′)], 7.36–7.39 [m, 3H, H(2′), H(4′), H(6′)], 7.67 [ddd, 1H, H(4), ^oJ 8.5, 7.3 Hz, ^mJ 1.6 Hz], 8.2 (br. s, 2H, NH, OH). ^{1}H NMR (400 MHz, [$^2H_6$]DMSO) δ: 4.52 (s, 2H, CH_2), 6.71 [dd, 1H, H(6), ^oJ 8.0 Hz, ^mJ 1.6 Hz], 6.81 [ddd, 1H, H(5), ^oJ 8.0, 7.4 Hz, ^mJ 1.1 Hz], 6.97 [dd, 1H, H(3), ^oJ 8.3 Hz, ^mJ 0.9 Hz], 7.26–7.39 (m, 5H, Ph), 7.39 [ddd, 1H, H(4), ^oJ 8.3, 7.4 Hz, ^mJ 1.6 Hz], 14.22 (s, 1H, NH), 16.7 (br. s, 1H, OH). IR (Vaseline oil, ν/cm^{-1}): 1675, 1610. Found (%): C, 58.98; H, 3.78; N, 16.13. Calc. for $C_{17}H_{13}F_3N_4O$ (%): C, 58.96; H, 3.78; N, 16.18.

2-[Benzylimino-(1,2,3-triazol-4-yl)methyl]-4-methylphenol **7b** was prepared from compound **5b** analogously to **7a**. Yield 55%, mp 215–216 °C (ethanol–H_2O, 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.15 (s, 3H, Me), 4.47 (br. s, 2H, CH_2), 6.38 [br. d, 1H, H(6), ^mJ 1.5 Hz], 6.93 [d, 1H, H(3), ^oJ 8.4 Hz], 7.15 [dd, 1H, H(4), ^oJ 8.4 Hz, ^mJ 1.9 Hz], 7.24–7.36 (m, 5H, Ph), 13.8 (br. s, 1H, NH). IR (Vaseline oil, ν/cm^{-1}): 1675, 1615, 1580, 1535. Found (%): C, 60.14; H, 4.18; N, 15.49. Calc. for $C_{18}H_{15}F_3N_4O$ (%): C, 60.00; H, 4.20; N, 15.55.



5–7: **a** R = H, R′ = CH_2Ph
b R = Me, R′ = CH_2Ph
c R = H, R′ = $(CH_2)_2OH$
d R = Me, R′ = $(CH_2)_2OH$
8: **a** R = H
b R = Me

Scheme 2

strong bases, undergo protonation at the imine nitrogen atom[20] in the presence of AcOH and generate iminium cations **5′**, which participate in the reaction. This hypothesis was supported by the fact that compounds **5** did not react with NaN_3 in ethanol without adding AcOH.

Salicyloyltriazoles **8a**,**b**,§ which cannot be synthesised from corresponding chromones **1**, were isolated upon the hydrolysis of imines **7a**,**b** under the action of an aqueous-ethanol solution of HCl. These compounds can be more conveniently prepared from chromenimines **5c**,**d** without the stage of the separation of easily hydrolysable imines **7c**,**d** with 2-hydroxyethyl groups. Because the transformations **6** → **5** and **5** → **7** occur *via* common intermediate **5′**, it is reasonable to suggest that compounds **6** would give ketones **8** upon the treatment with NaN_3 and AcOH. Indeed, we found that aminoenones **6c**,**d**, as well as chromenimines **5c**,**d**, give salicyloyltriazoles **8a**,**b** under analogous conditions.¶

Thus, we developed a simple and efficient synthetic procedure for 4(5)-salicyloyl-5(4)-trifluoromethyl-1,2,3-triazoles and their imines. These compounds are of considerable interest because the biological activity of triazole ketones is well known.[4]

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§ *4(5)-Salicyloyl-5(4)-trifluoromethyl-1,2,3-triazole* **8a**. A mixture of aminoenone **6c** (0.50 g, 1.8 mmol) and NaN_3 (0.24 g, 3.7 mmol) in 2 ml of AcOH–EtOH (1:1) was heated at 80 °C for 2 h. Next, 1 ml of 50% ethanol and five drops of concentrated HCl were added to the reaction mixture. The resulting solution was refluxed for 5 min; thereafter, the mixture was stirred with 10 ml of water. The precipitate was filtered off, washed with water, dried and recrystallised. Yield 73%, mp 150–151 °C (hexane–toluene, 1:2). Ketone **8a** in 77% yield was prepared by a similar procedure from compound **5c** on heating for 10 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.96 [ddd, 1H, H(5), ^oJ 8.2, 7.2 Hz, ^mJ 1.1 Hz], 7.09 [dd, 1H, H(3), ^oJ 8.6 Hz, ^mJ 1.1 Hz], 7.58 [ddd, 1H, H(4), ^oJ 8.6, 7.2 Hz, ^mJ 1.7 Hz], 8.11 [dd, 1H, H(6), ^oJ 8.2 Hz, ^mJ 1.7 Hz], 11.84 (s, 1H, NH), 12.5 (br. s, 1H, OH). IR (Vaseline oil, ν/cm^{-1}): 3350, 1635, 1605, 1565, 1520. Found (%): C, 46.67; H, 2.21; N, 16.29. Calc. for $C_{10}H_6F_3N_3O_2$ (%): C, 46.70; H, 2.35; N, 16.29.

4(5)-(2-Hydroxy-5-methylbenzoyl)-5(4)-trifluoromethyl-1,2,3-triazole **8b** was prepared from aminoenone **6d** analogously to **8a**; however, the heating was performed for 6 h. Yield 79%, mp 125–126 °C (hexane–toluene, 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.30 (s, 3H, Me), 7.00 [dd, 1H, H(3), ^oJ 8.5 Hz], 7.40 [dd, 1H, H(4), ^oJ 8.5 Hz, ^mJ 2.0 Hz], 7.83 [br. d, 1H, H(6), ^mJ 1.2 Hz], 11.68 (s, 1H, NH), 12.5 (br. s, 1H, OH). IR (Vaseline oil, ν/cm^{-1}): 3365, 3340, 1675, 1630, 1600, 1580, 1530. Found (%): C, 48.99; H, 3.05; N, 15.58. Calc. for $C_{11}H_8F_3N_3O_2$ (%): C, 48.72; H, 2.97; N, 15.49.

¶ Note that the ^{1}H NMR spectra of imines **7a**,**b** showed that all aromatic protons are shielded in both $CDCl_3$ and [$^2H_6$]DMSO solutions, as compared with ketones **8a**,**b**. The signal of the H(6) proton was most significantly upfield shifted (by almost 1.5 ppm); this is likely due to the arrangement of a triazole ring out of the molecular plane because of unfavourable steric interactions with the benzyl group. In this case, the 2-hydroxyaryl substituent and the imino group lie in the same plane because of a strong intramolecular hydrogen bond between the phenol proton and imine nitrogen (δ_{OH} 16.7 ppm in [$^2H_6$]DMSO).