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SHORT COMMUNICATIONS

Reactions of 2-(trifluoroacetyl)chromones with aromatic amines

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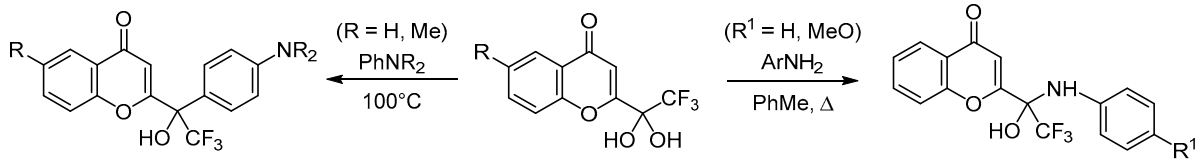


Aromatic amines reacted with 2-(trifluoroacetyl)chromones as C- or N-nucleophiles, depending on the conditions. When the reaction was performed under solvent-free conditions at 100°C for 12–18 h, they acted as C-nucleophiles and gave bishetarylcarbinols in 21–67% yields, while in refluxing toluene the addition of primary arylamines occurred *via* the amino group, providing the corresponding hemiaminals (80–86%).

Keywords: anilines, bishetarylcarbinols, hemiaminals, 2-(trifluoroacetyl)chromones.

Despite the rarity of fluorine-containing organic molecules in living nature, the trifluoromethyl group is one of the most valuable functional groups in synthetic and medicinal chemistry. The importance of this group is associated with the fact that many trifluoromethylated compounds show a variety of useful properties and find many applications in medicine and agriculture.[1] Their synthesis is often based on the use of CF_3-containing building blocks with relatively low molecular mass, which also must be sufficiently reactive and readily available.[2,3]

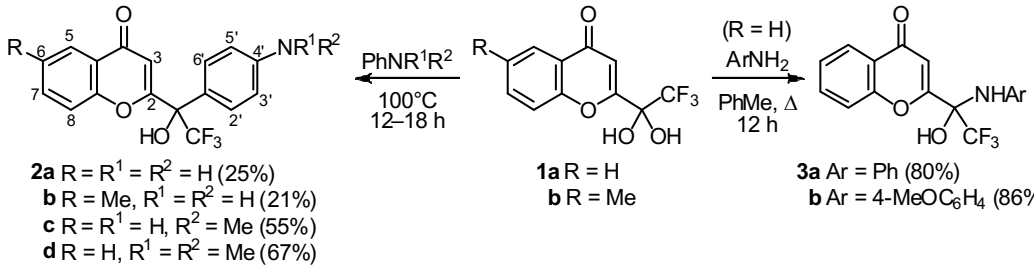
We have recently described a synthesis of 2-(trifluoroacetyl)chromones, which clearly meet these requirements and easily react with 1,2-diamines, forming partially fluorinated 5,6-dihydropyrazines and quinoxalines.[4] Besides that, indole and its methyl derivatives can add at the trifluoroacetyl moiety of these chromones with the formation of bishetarylcarbinols.[5] Similar reactions have been interpreted in the literature as electrophilic oxyalkylation of indoles and other 5-membered hetero-cycles.[6]

Due to the fact that the synthetic potential of 2-(trifluoroacetyl)chromones has not yet been thoroughly explored, our goal in the current work was to study for the first time their interactions with aromatic amines. On the basis of results reported by authors from Ukraine, who demonstrated that primary, secondary, and tertiary aromatic amines reacted with 2-(trifluoroacetyl)-1,3-benzothiazole according to the scheme of *ortho*/*para* oxyalkylation,[7] it could have been expected that anilines also should behave as C-nucleophiles in reactions with 2-(trifluoroacetyl)-chromones.

Indeed, we found that 2-(trifluoroacetyl)chromones, which existed as covalent hydrates **1a**,**b** (R = H, Me) due to the strongly electrophilic nature of the CF_3CO group,[4] reacted with aniline, *N*-methyl- and *N*,*N*-dimethylanilines (3.5 equiv) in the absence of solvent at 100–105°C over 12–18 h and gave bishetarylcarbinols **2a**–**d** in 21–67% yields. Thus, the reaction proceeded as electrophilic *para* oxyalkylation of anilines, which served the role of C-nucleophiles in this case (Scheme 1).

The yields of aniline adducts **2a**,**b** were merely 21–25% and could not be improved by increasing the reaction duration to 40 h. Compared to the reaction with aniline, the yields of reactions with *N*-methyl- and *N*,*N*-dimethylanilines were substantially higher (55–67%), which apparently can be explained by the more pronounced electron-donating character of the benzene ring. When attempting to extend the series of carbinols **2** by using 6-chloro- and 6-bromo-2-(trifluoroacetyl)chromones in the

Scheme 1



reaction with aromatic amines upon heating for 20 h, mainly the starting chromones were isolated, along with 2 to 6% of the target products (estimated from the data of ^{19}F NMR spectroscopy).

It is interesting to note that when the reaction conditions were changed and chromone **1a** was refluxed in toluene with aniline or *p*-anisidine (1.5 equiv) for 12 h, hemiaminals **3a**,**b** were formed in 80 and 86% yields, respectively, *via* the addition of aniline amino group at the trifluoroacetyl substituent (Scheme 1). These compounds were reasonably stable during storage, but partially decomposed to the starting materials when maintained in DMSO solution. It should be noted that *N*-methyl- and *N*,*N*-dimethylanilines under these conditions practically did not react with chromones **1a**, which was isolated in unchanged form together with 5–6% of carbinols **2c**,**d** (estimated from the data of ^{19}F NMR spectroscopy). At the same time, it has been reported that aromatic amines of various structures behaved as C-nucleophiles upon heating in toluene with 2-(trifluoroacetyl)-1,3-benzothiazole and reacted only at the benzene ring.[7] We propose that the decreased reactivity of chromones **1** compared to 2-(trifluoroacetyl)-1,3-benzothiazole can be caused by their existence in hydrate form.

The structure of the obtained compounds was established on the basis of high-resolution mass spectrometry, IR spectroscopy, as well as ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy. Comparing ^{1}H NMR spectra of isomers **2a** and **3a** showed, as should have been expected, that the otherwise similar chemical shifts of chromone ring protons were significantly altered by the presence of aniline ring. The difference in chemical shifts of the OH group protons was 0.42 ppm and was explained by the appearance of an additional σ-electron acceptor (nitrogen atom) at the carbinol center of compound **3a**, leading to enhancement of the intermolecular hydrogen bonds with solvent molecules. ^{19}F NMR spectra of isomers **2a** and **3a** showed signals of the CF_3 group at 89.4 and 83.1 ppm, respectively (Fig. 1).

Thus, aromatic amines participated in reactions with 2-(trifluoroacetyl)chromones as ambident nucleophiles and, depending on the reaction conditions, reacted at the *para* position of benzene ring (primary, secondary, and tertiary arylamines as C-nucleophiles under solvent-free conditions) or provided their amino group as a reactive site (primary arylamines as N-nucleophiles upon heating in toluene).

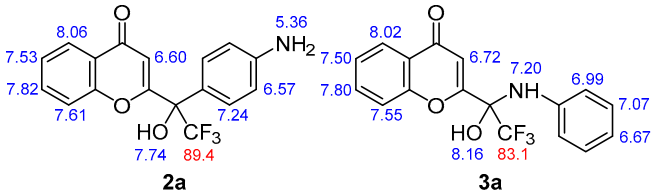


Figure 1. ^{1}H and ^{19}F NMR data for compounds **2a** and **3a** (DMSO-d_6, δ, ppm).

Experimental

IR spectra were recorded on a PerkinElmer Spectrum BX-II instrument by using an ATR accessory. ^{1}H, ^{19}F, and ^{13}C NMR spectra were acquired on a Bruker Avance II spectrometer (400, 376, and 100 MHz, respectively) in DMSO-d_6 relative to solvent signals (2.49 and 39.5 ppm for ^{1}H and ^{13}C nuclei, respectively); the internal standard for ^{19}F NMR spectra was C_6F_6. Melting points were determined on an SMP30 apparatus.

The starting 2-(trifluoroacetyl)chromones **1a**,**b** were obtained according to a published procedure.[4]

Synthesis of compounds 2a–d from chromones 1a,**b and anilines** (General method). A mixture of 2-(trifluoroacetyl)chromone hydrate **1a**,**b** (0.4 mmol) and the appropriate aniline (1.4 mmol) was heated on a glycerol bath to 100–105°C for 12–18 h. The reaction mixture was then cooled to room temperature, diluted with 95% ethanol (2 ml), the precipitate was filtered off and washed with ethanol (1 ml), providing compounds **2a**–**d** as yellow powders.

2-[1-(4-Aminophenyl)-1-hydroxy-2,2,2-trifluoroethyl]-4*H*-chromen-4-one (2a). Yield 49 mg (25%), mp 229–230°C. IR spectrum, ν, cm^{-1}: 3288, 1636, 1617, 1584, 1568, 1482. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.36 (2H, br. s, NH_2); 6.57 (2H, d, *J* = 8.6, H-3',5'); 6.60 (1H, s, 3-CH); 7.24 (2H, d, *J* = 8.6, H-2',6'); 7.53 (1H, td, *J* = 7.6, *J* = 0.8, H-6); 7.61 (1H, d, *J* = 8.5, H-8); 7.74 (1H, s, OH); 7.82 (1H, ddd, *J* = 8.5, *J* = 7.2, *J* = 1.6, H-7); 8.06 (1H, dd, *J* = 7.9, *J* = 1.6, H-5). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 77.1 (q, $^{2}J_{CF}$ = 28.7); 109.7; 113.3; 118.4; 121.8 (d, $^{3}J_{CF}$ = 1.8); 123.0; 124.4 (q, $^{1}J_{CF}$ = 287.6); 124.9; 126.0; 127.5; 134.8; 149.5; 155.4; 165.6; 176.7. ^{19}F NMR spectrum, δ, ppm: 89.4 (s, CF_3). Found, *m*/*z*: 336.0839 $[M+H]^+$. $C_{17}H_{13}F_3NO_3$. Calculated, *m*/*z*: 336.0832.

2-[1-(4-Aminophenyl)-1-hydroxy-2,2,2-trifluoroethyl]-6-methyl-4*H*-chromen-4-one (2b). Yield 36 mg (21%), mp 235–236°C. IR spectrum, ν, cm^{-1}: 3433, 3377, 3260, 3191, 3074, 2776, 2668, 1643, 1615, 1576, 1515, 1500, 1483. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.43 (3H, s,

CH_3); 5.36 (2H, br. s, NH_2); 6.56 (2H, d, *J* = 8.6, H-3',5'); 6.57 (1H, s, 3-CH); 7.22 (2H, d, *J* = 8.6, H-2',6'); 7.51 (1H, d, *J* = 8.6, H-8); 7.64 (1H, dd, *J* = 8.6, *J* = 2.2, H-7); 7.72 (1H, s, OH); 7.84 (1H, d, *J* = 2.0, H-5). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 20.4; 77.1 (q, $^2J_{CF}$ = 28.6); 109.6; 113.2; 118.2; 121.8; 122.8; 124.1; 124.5 (q, $^1J_{CF}$ = 287.7); 127.5; 128.7; 135.8; 149.5; 153.7; 165.5; 176.7. ^{19}F NMR spectrum, δ, ppm: 89.3 (s, CF_3). Found, *m*/*z*: 350.0988 $[M+H]^+$. $C_{18}H_{15}F_3NO_3$. Calculated, *m*/*z*: 350.0999.

2-[1-Hydroxy-1-(4-methylaminophenyl)-2,2,2-trifluoroethyl]-4*H*-chromen-4-one (2c). Yield 70 mg (55%), mp 176–177°C. IR spectrum, ν, cm^{-1}: 3241, 3111, 2932, 2905, 2823, 1634, 1574, 1532, 1480. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.66 (3H, d, *J* = 4.7, CH_3); 5.94 (1H, q, *J* = 4.7, NH); 6.55 (2H, d, *J* = 8.7, H-3',5'); 6.60 (1H, s, 3-CH); 7.31 (2H, d, *J* = 8.7, H-2',6'); 7.53 (1H, t, *J* = 7.5, H-6); 7.60 (1H, d, *J* = 8.4, H-8); 7.77 (1H, s, OH); 7.82 (1H, ddd, *J* = 8.6, *J* = 7.2, *J* = 1.6, H-7); 8.06 (1H, dd, *J* = 7.9, *J* = 1.6, H-5). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 29.4; 77.1 (q, $^2J_{CF}$ = 28.6); 109.7; 111.1; 118.4; 121.5; 123.0; 124.9; 126.0; 127.3 (q, $^1J_{CF}$ = 287.5); 127.5; 134.8; 150.4; 155.4; 165.6; 176.7. ^{19}F NMR spectrum, δ, ppm: 89.3 (s, CF_3). Found, *m*/*z*: 350.1007 $[M+H]^+$. $C_{18}H_{15}F_3NO_3$. Calculated, *m*/*z*: 350.0999.

2-[1-Hydroxy-1-(4-dimethylaminophenyl)-2,2,2-trifluoroethyl]-4*H*-chromen-4-one (2d). Yield 142 mg (67%), mp 198–199°C. IR spectrum, ν, cm^{-1}: 3272, 2905, 2819, 1641, 1614, 1569, 1531, 1464. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.90 (6H, s, $2CH_3$); 6.61 (1H, s, 3-CH); 6.74 (2H, d, *J* = 9.0, H-3',5'); 7.40 (2H, d, *J* = 9.0, H-2',6'); 7.53 (1H, t, *J* = 7.6, H-6); 7.61 (1H, d, *J* = 8.5, H-8); 7.82 (1H, ddd, *J* = 8.5, *J* = 7.3, *J* = 1.6, H-7); 7.84 (1H, s, OH); 8.06 (1H, dd, *J* = 7.9, *J* = 1.5, H-5). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 39.7; 77.1 (q, $^2J_{CF}$ = 28.8); 109.7; 111.6; 118.3; 122.0; 123.0; 124.4 (q, $^1J_{CF}$ = 288.1); 124.9; 126.0; 127.4; 134.7; 150.6; 155.4; 165.4; 176.6. ^{19}F NMR spectrum, δ, ppm: 89.3 (s, CF_3). Found, *m*/*z*: 364.1161 $[M+H]^+$. $C_{19}H_{16}F_3NO_3$. Calculated, *m*/*z*: 364.1155.

2-(1-Anilino-1-hydroxy-2,2,2-trifluoroethyl)-4*H*-chromen-4-one (3a). A solution of 2-(trifluoroacetyl)chromone (**1a**) (150 mg, 0.58 mmol) and aniline (80 mg, 0.86 mmol) in toluene (5 ml) was refluxed for 12 h and left overnight. The precipitate that formed was filtered off and washed with toluene (1 ml). Yield 155 mg (80%), white powder, mp 137–138°C. IR spectrum, ν, cm^{-1}: 3339, 3201, 3120, 3060, 1638, 1598, 1571, 1531, 1501, 1483. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.67 (1H, t, *J* = 7.3, H-4'); 6.72 (1H, s, 3-CH); 6.99 (2H, d, *J* = 7.7, H-2',6'); 7.07 (2H, t, *J* = 7.9, H-3',5'); 7.20 (1H, s, NH); 7.50 (1H, t, *J* = 7.6, H-6); 7.55 (1H, d, *J* = 8.5, H-8); 7.80 (1H, ddd, *J* = 8.5, *J* = 7.2, *J* = 1.5, H-7); 8.02 (1H, dd, *J* = 7.9, *J* = 1.5, H-5); 8.16 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 83.2 (q, $^2J_{CF}$ = 30.6); 112.3; 113.8; 116.2; 118.3; 119.0; 122.9 (q, $^1J_{CF}$ = 290.6); 125.9; 126.0; 128.5; 134.8; 143.8; 148.5; 162.3; 176.5. ^{19}F NMR spectrum, δ, ppm: 83.1 (s, CF_3). Found, *m*/*z*: 336.0844 $[M+H]^+$. $C_{17}H_{13}F_3NO_3$. Calculated, *m*/*z*: 336.0842.

2-{1-Hydroxy-1-[(4-methoxyphenyl)amino]-2,2,2-trifluoroethyl}-4*H*-chromen-4-one (3b) was obtained from chromone **1a** and anisidine analogously to the procedure for preparation of compound **3a**. Yield 123 mg (86%), yellow powder, mp 134–135°C. IR spectrum, ν, cm^{-1}: 3356, 3187, 2838, 1637, 1599, 1569, 1515, 1483, 1467. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.59 (3H, s, CH_3); 6.66 (1H, s, 3-CH); 6.68 (2H, d, *J* = 9.0, H-3',5'); 6.74 (1H, br. s, NH); 6.96 (2H, d, *J* = 9.0, H-2',6'); 7.50 (1H, ddd, *J* = 7.9, *J* = 7.2, *J* = 0.7, H-6); 7.57 (1H, d, *J* = 8.4, H-8); 7.81 (1H, ddd, *J* = 8.4, *J* = 7.2, *J* = 1.6, H-7); 8.01 (1H, dd, *J* = 7.9, *J* = 1.6, H-5); 8.06 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 54.9; 83.8 (q, $^2J_{CF}$ = 30.4); 112.2; 113.9; 114.9; 118.4; 124.1 (q, $^1J_{CF}$ = 294.4); 124.9; 126.0; 128.2; 128.9; 136.4; 153.1; 155.6; 162.6; 176.6. ^{19}F NMR spectrum, δ, ppm: 83.4 (s, CF_3). Found, *m*/*z*: 366.0953 $[M+H]^+$. $C_{18}H_{15}F_3NO_4$. Calculated, *m*/*z*: 366.0948.

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