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Domino Transformations of *gem*-Trifluoroacetyl(bromo)alkenes under the Action of Secondary Amines

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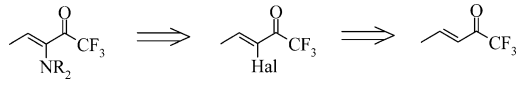
2-Bromo-3-arylpropenyl trifluoromethyl ketones underwent aza-Michael/hydroxyalkylation domino reactions triggered by secondary amines to give unexpectedly 2-amino-1-trifluoromethyl indenols in good yields. The process was found to involve the intermediate formation of captodative aminoalkenes. Treatment of 2-bromo-3-thienyl derivatives with the same nucleophiles afforded the captodative trifluoroacetyl(amino)alkenes. The indenols obtained in this reaction can be converted into the corresponding indanones by acid hydrolysis.

Introduction

Captodative carbonyl-containing aminoalkenes have increasing interest to synthetic organic chemists.[1] Their attraction is caused by remarkable and specific reactivity that is different from simple enamines and α,β-unsaturated aldehydes, ketones, and esters. These unique kinds of enamines have been used as versatile building blocks in the synthesis of various biologically important heterocycles and analogs of natural substances. It is well known that the introduction of fluorine atoms in organic molecules often produces dramatic modifications of the chemical properties and biological activity of parent compounds.[2] Thus, trifluoromethylated derivatives are of great interest in various fields of applications as shown, for example, by the number of CF_3-containing drugs.[3] That is why the development of new fluorinated building blocks is always required. Recently, considerable attention has been given to the fluorine-bearing derivatives of enamines.[4] In the context of our going interest in the chemistry of captodative aminoalkenes and in search of the synthesis of fluorinated building blocks and analogs of bioactive compounds, we turned our attention to the enamines bearing a trifluoroacetyl group at the *gem* position. The symbiosis of the enamine and perfluoroacyl moieties is of considerable theoretical, synthetic, and pharmacological interest. To the best of our knowledge, this type of compound has not yet been studied. In contrast, the chemistry of, in general, α,β-unsaturated trifluoromethyl ketones and, in particular, push–pull trifluoromethyl aminoenones was strongly developed last decade and is well documented.[5]

The most straightforward route for the preparation of captodative trifluoroacetyl(amino)alkenes is substitution of a particular leaving group by an amino one. Because halide ions are one of the best nucleophiles, the corresponding α-halo-α,β-unsaturated trifluoromethyl ketones can serve as key intermediates. Therefore, a retrosynthetic approach for the target compounds considers the introduction of the halogen atom at the α-position as the initial step, followed by its nucleophilic substitution with a secondary amine as the second step (Scheme 1). This strategy is universal and very attractive because of its experimental simplicity and availability of the starting compounds. Previously, this methodology was successfully applied to the synthesis of various captodative aminoalkenes containing a carbonyl-, formyl-, or alkoxycarbonyl functional group[1,6] as an electron-withdrawing group and including derivatives having a slow basic tertiary amino group as well as a terminal double bond.[7] It is interesting to remark that only the β-alkoxy group has been regiospecifically substituted with secondary or primary amines in their reactions with β-butoxy-α-bromovinyl trifluoromethyl ketone.[5e] In this paper we describe our synthetic efforts to synthesize captodative trifluoroacetyl(amino)alkenes.



Scheme 1. Retrosynthetic route to captodative trifluoroacetyl(amino)alkenes.

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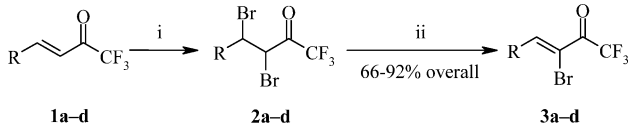
Results and Discussion

The required starting materials − trifluoroacetyl(bromo)-alkenes **3a**–**d** − were prepared in high overall yields after a two-step procedure involving the reaction of readily available trifluoromethyl alkenyl ketones **1a**–**d**[8] with bromine in anhydrous $CHCl_3$, and subsequent dehydrobromination of intermediate dibromo derivatives **2a**–**d** by Et_3N in dry ether (Scheme 2).



R = Ph (**a**), 4-$MeOC_6H_4$ (**b**), 2,5-$(MeO)_2C_6H_3$ (**c**), 2-thienyl (**d**)

Scheme 2. Reagents and conditions: (i) Br_2, 0 °C, $CHCl_3$; (ii) Et_3N, 10 °C, Et_2O.

Ketones **3a**–**d** were identified as a single geometric isomer. Their (*Z*) configuration was established by the concerted application of a ^1H–^1H 2D NOESY homonuclear experiment and also a ^1H–^{13}C 2D HMBC heteronuclear experiment for bromo derivatives **3c**,**d** (Figure 1). In fact, the spectrum of ketone **3c** contains only one NOE peak between the resonance of the olefinic proton and the protons of methoxy group in the 2-position, whereas no correlations are seen between the proton of the CH= group and any aromatic signals. The methoxy group in the 5-position has NOE interactions with both the 4- and 6-aromatic protons. The presence of a quite intensive cross peak between the olefinic proton and the $=C^3$–H proton of the thienyl moiety was revealed in compound **3d**. This fact led us to the conclusion that the bromine atom and aromatic (for **3c**) or thienyl (for **3d**) moieties are arranged in a (*Z*) configuration. The geometry of these ketones was elucidated also by comparison of the vicinal coupling constant between the carbonyl C atom and the olefinic proton ($^3J_{C-H}$ = 6.0 and 5.2 Hz for compounds **3c** and **3d**, respectively). It is known that this constant lie between 0 and 6 Hz for the s-*cis* isomer and between 9 and 14 Hz for the s-*trans* isomer.[9] The additional arguments have been received from the analysis of their IR spectra: the intensity ratio observed for the C=O and C=C stretching bands suggests a s-*cis* conformation of the C=C–C=O fragment.[10]

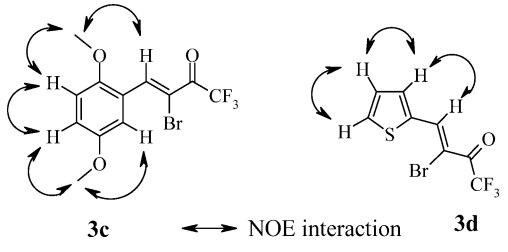
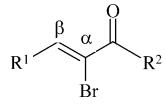


Figure 1. Relative stereochemistry of bromoenones **3c**,**d**.

According to the classical scheme now generally accepted, the reaction of nucleophiles with haloalkenes bearing an electron-withdrawing group (EWG) at the *gem* position does not proceed through direct substitution and in fact presents as a Michael addition–substitution–elimination domino sequence, Ad–S_N–E.[11] Consequently, an increase in the EWG acceptor ability should be favorable to the first step of the reaction − the aza-Michael addition. The ^{13}C NMR chemical shift differences between adjacent olefinic carbon atoms can serve as a reliable parameter of double bond polarization.[12] On the basis of the data in Table 1, it was expected that bromoalkenes bearing a trifluoroacetyl group would be the most active Michael acceptors. Indeed, it was reported earlier that unsubstituted trifluoromethyl alkenyl ketones are highly reactive species toward nucleophilic addition reactions.[13]

Table 1. The relationship between the chemical shift differences (C_β–C_α) and the nature of the electron-withdrawing group of bromoalkenes.

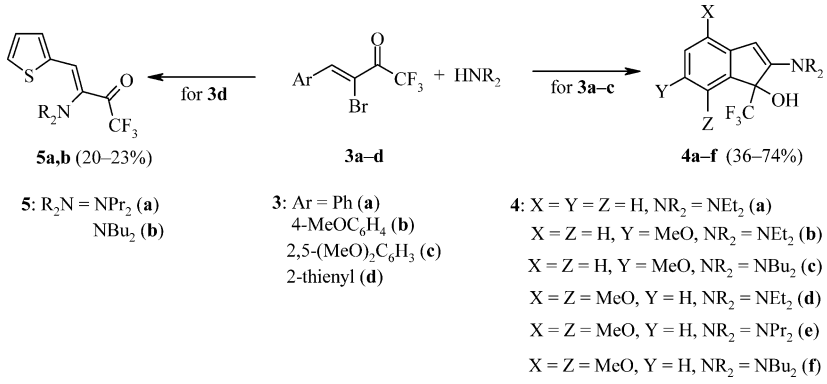


Entry	R^1	R^2	Δ (δ C_β − δ C_α)
1	4-$MeOC_6H_4$	CF_3	33.21
2	Ph	CF_3	30.30
3	thienyl	CF_3	26.80
4	2,5-$(MeO)_2C_6H_3$	CF_3	25.82
5	Ph	H	24.32[14]
6	Ph	Ph	20.08[14]

We found that the reaction of bromoenones **3a**–**d** with secondary amines (2 equiv.) readily proceeds under mild conditions (room temperature, without catalyst). Unfortunately, attempts to prepare the target captodative trifluoromethyl(amino)alkenes in the case of enones **3a**–**c** failed. Surprisingly, the only isolated products, formed in good yield, were indenols **4a**–**e** (Scheme 3). Their structure was confirmed by spectroscopic methods. The ^1H NMR spectra of indenols **4a**–**e** show a singlet for the olefinic proton at δ = 5.25–5.45 ppm. In the ^{13}C NMR spectra of these compounds, a signal for the carbonyl group is absent. Instead, a quadruplet of a quaternary carbon atom joined to a CF_3 moiety appears at δ = 83–86 ppm (J = 30 Hz). An alternative structure of 3-amino-substituted indenol was excluded by additional NMR spectroscopic experiments. Thus, according to the 2D NOESY NMR spectrum of **4d**, there are off-diagonal peaks between the olefinic proton and the signals for both the MeO and NCH_2 groups, which indicates the α-position of the amino functionality.

It should be noted that the result depends on the nature of the solvent. For example, whereas the reaction of ketone **3a** with diethylamine in ethanol gives a complex mixture of products, the use of ether or THF as solvent leads to the formation of indenol **4a** as a major (or single) product.

Indenols, as is well known, are an important type of organic compounds that attract the attention of both synthetic and pharmaceutical chemists.[15] Despite this fact, few methods have been proposed for the synthesis of these derivatives and, as a rule, transition-metal-catalyzed coupling reactions have been employed. So, this reaction is very efficient for the preparation of functionalized 1-trifluoro-



Scheme 3. Reagents and conditions: HNR_2, Et_2O or THF, r.t.

methyl-1-indenols. However, when the reaction was carried out with bromoenone **3d**, the corresponding indenol derivatives were not obtained at all. It is known that the formation of a five-membered ring condensed with thiophene does not proceed very easily. To contrast to enones **3a**–**c**, bromoketone **3d** was treated with dipropylamine or dibutylamine to give target captodative aminoalkenes **5a**,**b** (Scheme 3). The moderate yields of aminoalkenes **5a**,**b** probably can be explained by the side reactions (polymerization, hydrolysis, etc.) due to the instability of these derivatives. According to ^1H and ^{13}C NMR spectra, these compounds exist as a single isomer. The value of the vicinal coupling constant between the carbon atom of the carbonyl group and the olefinic proton ($^3J_{C–H}$ = 5.7 Hz) as well as NOE experiments led us to the conclusion that aminoenones **5a**,**b** have the same (*Z*) configuration as initial bromoenone **3d** (Figure 2).

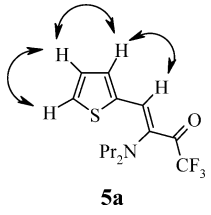
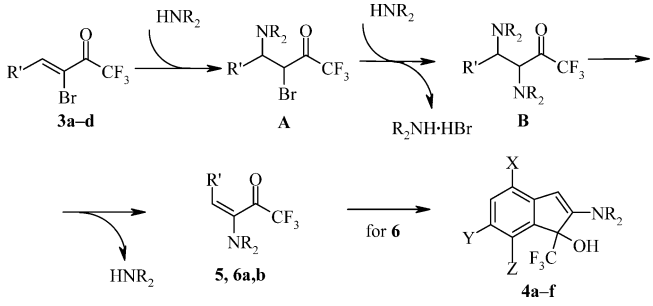


Figure 2. Relative stereochemistry of aminoenone **5a**.

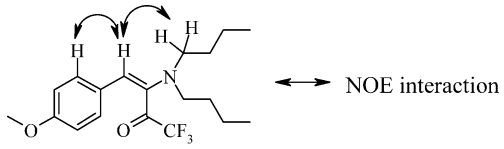
As we have mentioned, this reaction does not proceed through direct halogen substitution. On the basis of the results and known nucleophilic vinylic substitution in *gem*-activated haloalkenes, the following general sequence of transformations can be proposed to explain this reaction cascade (Scheme 4). A complete interpretation of the reaction mechanism is hampered because possible intermediates **A** and **B** were not isolated and their formation has not been recorded. However, we can suggest that the first step of these domino transformations includes aza-Michael addition to initial substrate **3**, further replacement of the halogen at the sp^3 carbon atom of saturated ketone **A**, and elimination of the secondary amine to give the product of *ipso* substitution. Unfortunately, derivatives **5**, **6a**–**e** could not be isolated, but they could be detected by ^1H and ^{13}C NMR spectroscopy of the crude reaction mixture. The following hydroxyalkylation reaction of intermediates **6a**–**f** leads directly to final indenols **4a**–**f**. The influence of the trifluoromethyl group on such a result is quite clear. The strong electron-withdrawing character of the CF_3 moiety activates the carbonyl group and then favors the hydroxyalkylation reaction.



Scheme 4. Reaction cascade Ad–S_N–E–cyclization.

To provide further support for the postulated scheme, we monitored the reaction of ketones **3b**,**c** with dibutylamine and dipropylamine, respectively. In these cases, analysis of the reaction mixtures has shown that the first three steps were quite rapid reactions, whereas the cyclization reaction was a limiting step. In fact, the amine hydrobromide precipitate appeared within some minutes of the start of the reaction. Thus, when dibutylamine was treated with ketone **3b** for 15 h at room temperature, a mixture (10:1) of captodative aminoenone **6a** and corresponding indenol **4c** was recorded by ^1H NMR spectroscopy. We obtained both the ^1H and ^{13}C NMR spectra of intermediate **6a**. The captodative nature of this aminoenone[14a] is supported by comparison of the chemical shifts of the olefinic carbon atoms: the signal of the β atom is at higher field relative to that of the α atom (115.8 and 158.5 ppm, respectively). According to 2D NMR spectra (NOESY and HMBC), the geometry of intermediate **6a** is opposite to the configuration of captodative aminoenone **5a** and favorable to the cyclization into indenol **4c**. Thus, the signal of the carbonyl carbon atom appeared as a quartet of doublets with $^3J_{C–H}$ = 10.3 Hz and $^2J_{C–F}$ = 34.5 Hz, which indicates that aminoenone **6a** has the configuration shown in Figure 3. During the reaction, we observed that in the ^1H NMR spectra the

singlet for the olefinic proton of derivative **6a** (δ = 5.89 ppm) disappeared with the simultaneous appearance of a singlet for the olefinic proton of indenol **4c** (δ = 5.25 ppm). In the ^{13}C NMR spectrum, the quadruplet of the carbonyl group of intermediate **6a** was observed at δ = 186.9 ppm. Its disappearance after some hours and the appearance of the signal for the quaternary carbon atom $C(OH)CF_3$ as a quadruplet at δ = 83.0 ppm proved the transformation of linear aminoenone **6a** to cyclic derivative **4c**. The same sequence of transformations was recorded by NMR spectroscopy during the monitoring of the reaction of ketone **3c** with dipropylamine.



6a

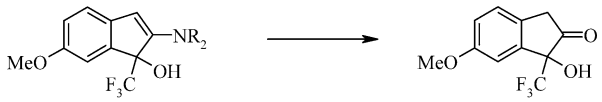
Figure 3. Relative stereochemistry of aminoenone **6a**.

Moreover, we were fortunate to restrain the reaction at the first step and recorded the aza-Michael adduct. It is known that the *N*-trimethylsilyl derivatives of secondary amines react as nucleophiles, and thus they were used to determine the reaction mechanism.[16] We found that treatment of enone **3a** with trimethyl(diethylamino)silane under microwave conditions produce aza-Michael adduct **7**. In fact, in the ^1H NMR spectrum of the reaction mixture the signals of compound **7** are observed only: δ = 0.99 (t, J = 7.1 Hz, CH_3), 2.65 (q, J = 7.1 Hz, CH_2), 4.87 (s, CH), 7.25–7.55 (m, C_6H_5) ppm; ^{19}F NMR: δ = –58.23 ppm. So, the formation of silyl enol ether **7** may serve as strong proof for the suggested mechanism (Scheme 5). These results once more indicated that the reaction occurred through an aza-Michael addition–substitution–elimination–hydroxylation sequence.

3a **7**

Scheme 5. Reagent and conditions: Me_3SiNEt_2, microwave.

It is remarkable that indenols **4** exhibit properties of simple enamines; in particular, they are hydrolyzed to give the corresponding carbonyl derivatives (Scheme 6). Thus, indenols **4b**,**c** obtained from ketone **3b** and diethyl- and dibutylamine, respectively (without purification), were easily converted into indanone **8** by treatment with a solution of hydrochloric acid at room temperature over 2 h in an overall yield up to 68%.



R = Et (**4b**)
R = Bu (**4c**)

8 (47–68%)

Scheme 6. Reagents and conditions: H_2O/HCl, r.t.

Conclusion

We achieved the one-pot synthesis of indenol derivatives from easily available trifluoroacetyl(bromo)alkenes and secondary amines. Considering the importance of indenols as useful building blocks in the synthesis of natural compounds and their biological activity, we developed an efficient method for the synthesis of 1-trifluoromethyl-1-indenols. We attributed this unexpected result to the very easy intramolecular cyclization of intermediate captodative trifluoroacethyl(dialkylamino)alkenes. The latter can be detected in the reaction mixture and isolated in the case of β-thienyl-substituted derivatives. The results obtained in this study confirm our previous observations in the unpredictable chemistry of captodative carbonyl bearing enamines. Further development of this methodology and detailed studies of the properties of the captodative trifluoroacetyl(amino)alkenes and corresponding indenols are now in progress.

Experimental

General Remarks: ^1H, ^{13}C, ^{15}N, and ^{19}F NMR spectra were recorded with a Bruker AVANCE 400 MHz spectrometer for solutions in $CDCl_3$ or CD_3CN. Chemical shifts (δ) in ppm are reported by using residual chloroform (7.25 ppm for ^1H and 77.20 ppm for ^{13}C) or acetonitrile (1.94 ppm for ^1H and 1.40, 118.60 ppm for ^{13}C) as internal references. The coupling constants (J) are given in Hertz. The concerted application of ^1H–^1H 2D COSY[17] and NOESY[18] homonuclear experiments as well as ^1H–^{13}C 2D HSQC[19] and HMBC[20] heteronuclear experiments were used for the distinction of the carbon and proton resonances in all cases. The IR spectra were measured with a Specord IR-75 instrument. The GC–MS analyses were performed with a Hewlett–Packard HP 5971A instrument (EI, 70 eV). The silica gel used for flash chromatography was 230–400 mesh. All reagents were of reagent grade and were used as such or distilled prior to use. All the solvents were dried according to standard procedures and freshly distilled prior to use. Trifluoromethyl alkenyl ketones **1a**–**d** were prepared as reported previously.[5b,8]

General Procedure for the Bromination of Ketones 1a–d: Bromine (0.8 g, 5 mmol) in $CHCl_3$ (5 mL) was added dropwise over 30 min into a stirred solution of the ketone (5 mmol) in $CHCl_3$ (5 mL). During the addition, the temperature was kept at +10 °C. The mixture was then stirred at room temperature until the orange color did not fade away. The solvent was evaporated and a light-yellow solid appeared. The crude dibromo derivatives **2a**–**d** were found suitable for further transformation without any purification.

Triethylamine (0.5 g, 5 mmol) in anhydrous ether (10 mL) was added dropwise over 5 min into a stirred solution of dibromoketone **2** (5 mmol) in Et_2O (10 mL) at +10 °C. The mixture was kept at room temperature overnight and filtered. After the solvent was evaporated, α-bromoenones **3a**–**d** were obtained either by distillation at reduced pressure (**3a**,**b**) or column chromatography (**3c**,**d**).

3-Bromo-1,1,1-trifluoro-4-phenyl-3-buten-2-one (3a): Yield 90%. Yellow liquid, b.p. 100(3) °C. IR (KBr): $\tilde{\nu}$ = 1592 (C=C), 1712 (C=O) cm^{-1}. ^1H NMR (400.16 MHz, $CDCl_3$): δ = 7.40–7.55 (m, 3 H), 7.90–8.00 (m, 2 H), 8.17 (s, 1 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 116.04 (q, J = 291.4 Hz, CF_3), 116.96 (=C-Br), 128.98, 131.54, 132.23 (CH aryl), 133.17 (C aryl), 147.26 (q, J = 3.8 Hz, CH=), 175.91 (q, J = 35.3 Hz, C=O) ppm. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = –69.35 ppm. MS (EI): *m*/*z* (%) = 280 (25) $[M + 1]^+$, 278 (25) $[M – 1]^+$, 209, 211 (32), 181, 183 (14), 102 (100). $C_{10}H_6BrF_3O$ (279.06): calcd. C 43.04, H 2.17, Br 28.63, F 20.42; found C 42.87, H 2.25, Br 28.19, F 20.31.

3-Bromo-1,1,1-trifluoro-4-(4-methoxyphenyl)-3-buten-2-one (3b): Yield 86%. Pale yellow crystals, b.p. 142–143(1) °C, m.p. 45 °C. IR (KBr): $\tilde{\nu}$ = 1585 (C=C), 1692 (C=O) cm^{-1}. ^1H NMR (400.16 MHz, $CDCl_3$): δ = 3.85 (s, 3 H), 6.96 (d, J = 9.0 Hz, 2 H), 8.00 (d, J = 9.0 Hz, 2 H), 8.09 (s, 1 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 55.71 (OCH_3), 113.94 (=C-Br), 114.53 (CH aryl), 116.14 (q, J = 291.5 Hz, CF_3), 125.51 (C aryl), 134.37 (CH aryl), 147.15 (q, J = 3.7 Hz, CH=), 163.21 (C_{ar}-O), 176.20 (q, J = 35.0 Hz, C=O) ppm. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = –69.00 ppm. MS (EI): *m*/*z* (%) = 279 (2) $[M – MeO + 1]^+$, 277 (2) $[M – MeO – 1]^+$, 239, 241 (42), 132 (100), 89 (45). $C_{11}H_8BrF_3O_2$ (309.08): calcd. C 42.75, H 2.61, Br 25.85, F 18.44; found C 42.76, H 2.71, Br 26.24, F 18.06.

3-Bromo-4-(2,5-dimethoxyphenyl)-1,1,1-trifluoro-3-buten-2-one (3c): Yield 92%. Red crystals, m.p. 72 °C. IR (KBr): $\tilde{\nu}$ = 1570 (C=C), 1695 (C=O) cm^{-1}. ^1H NMR (400.16 MHz, $CDCl_3$): δ = 3.78 (s, 3 H), 3.84 (s, 3 H), 6.87 (d, J = 9.0 Hz, 1 H), 7.04 (dd, J = 9.0, 2.8 Hz, 1 H), 7.86 (d, J = 2.8 Hz, 1 H), 8.61 (s, 1 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 56.03, 56.52 (OCH_3), 112.13 (CH aryl), 114.85 (CH aryl), 116.05 (q, J = 291.8 Hz, CF_3), 116.93 (=C-Br), 120.01 (CH aryl), 122.43 (C aryl), 145.75 (q, J = 3.5 Hz, CH=), 153.08, 153.48 (C_{ar}-O), 176.14 (q, J = 34.9, ^3J = 6.0 Hz, C=O) ppm. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = –68.48 ppm. MS (EI): *m*/*z* (%) = 340 (100) $[M + 1]^+$, 338 (100) $[M – 1]^+$, 307, 309 (72), 175 (93), 69 (47). $C_{12}H_{10}BrF_3O_3$ (339.11): calcd. C 42.50, H 2.97, Br 23.56, F 16.81; found C 43.04, H 3.17, Br 23.55, F 16.57.

3-Bromo-1,1,1-trifluoro-4-(2-thienyl)-3-buten-2-one (3d): Yield 66%. Pale brown crystals, m.p. 34–35 °C. IR (KBr): $\tilde{\nu}$ = 1580 (C=C), 1700 (C=O) cm^{-1}. ^1H NMR (400.16 MHz, $CDCl_3$): δ = 7.25 (dd, J = 5.1, 3.9 Hz, 1 H), 7.72 (dd, J = 3.9, 1.0 Hz, 1 H), 7.82 (dd, J = 5.1, 1.0 Hz, 1 H), 8.43 (s, 1 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 113.66 (=C-Br), 116.09 (q, J = 291.5 Hz, CF_3), 128.00 (C-4), 135.47 (C-5), 137.40 (C-2), 139.07 (C-3), 140.46 (q, J = 3.3 Hz, CH=), 175.10 (q, J = 35.8, ^3J = 5.2 Hz, C=O) ppm. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = –68.43 ppm. MS (EI): *m*/*z* (%) = 286 (97) $[M + 1]^+$, 284 (97) $[M – 1]^+$, 215, 217 (100), 187, 189 (30), 108 (100), 69 (92). $C_8H_4BrF_3OS$ (285.08): calcd. C 33.71, H 1.41, Br 28.03, F 19.99; found C 33.90, H 1.55, Br 29.14, F 19.98.

General Procedure for the Reaction of Ketones 3a–d with Amines: A mixture of bromoketone **3a**–**d** and secondary amine (2 equiv.) in ether or THF was stirred at room temperature overnight. The solvent was removed, and the analytically pure samples of indenoles **4a**,**d**–**f**, aminoenones **5a**,**b**, or indanone **8** were obtained by further column chromatography (silica gel, ether/hexane).

The following compounds were obtained by this procedure.

2-(Diethylamino)-1-(trifluoromethyl)-1*H*-inden-1-ol (4a): Yield 55%. Oil. IR (KBr): $\tilde{\nu}$ = 1698 (C=C), 3510 (OH) cm^{-1}. ^1H NMR (400.16 MHz, $CDCl_3$): δ = 1.14 (t, J = 7.0 Hz, 6 H), 3.20–3.35 (m, 2 H), 3.45–3.60 (m, 2 H), 5.38 (s, 1 H), 5.55 (br. s, 1 H), 6.85–6.95 (m, 2 H), 7.15–7.35 (m, 2 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 12.31 (CH_3), 44.22 (NCH_2), 83.25 (q, J = 30.0 Hz, C-OH), 103.63 (CH=), 117.88, 122.11, 122.33, 122.97, 130.72 (CH aryl), 124.84 (q, J = 283 Hz, CF_3), 144.93 (C aryl), 152.42 (=C-N) ppm. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = –79.25 ppm. MS (EI): *m*/*z* (%) = 271 (78) $[M]^+$, 256 (100), 210 (17), 158 (18), 89 (33). $C_{14}H_{16}F_3NO$ (271.28): calcd. C 61.99, H 5.94, F 21.01, N 5.16; found C 62.07, H 6.01, F 20.67, N 5.01.

2-(Diethylamino)-6-methoxy-1-(trifluoromethyl)-1*H*-inden-1-ol (4b): ^1H NMR (400.16 MHz, $CDCl_3$): δ = 1.12 (t, J = 7.5 Hz, 6 H), 3.15–3.30 (m, 2 H), 3.35–3.50 (m, 2 H), 3.77 (s, 3 H), 5.34 (s, 1 H), 6.70 (dd, J = 2.4, 8.0 Hz, 1 H), 6.78 (d, J = 8.0 Hz, 1 H), 7.00 (d, J = 2.4 Hz, 1 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 11.82 (CH_3), 43.77 (NCH_2), 55.44 (OCH_3), 82.91 (q, J = 29.6 Hz, C-OH), 104.00 (CH=), 111.15 (C-7), 114.51 (C-5), 117.84 (C-4), 124.60 (q, J = 285 Hz, CF_3), 137.29 (C-9), 138.67 (C-8), 150.91 (=C-N), 155.66 (C_{ar}-O) ppm. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = –78.55 ppm.

2-(Dibutylamino)-6-methoxy-1-(trifluoromethyl)-1*H*-inden-1-ol (4c): ^1H NMR (400.16 MHz, $CDCl_3$): δ = 0.90 (t, J = 7.5 Hz, 6 H), 1.25–1.40 (m, 4 H), 1.45–1.60 (m, 4 H), 2.95–3.10 (m, 2 H), 3.50–3.65 (m, 2 H), 3.70 (s, 3 H), 5.25 (s, 1 H), 6.65 (dd, J = 2.4, 8.0 Hz, 1 H), 6.73 (d, J = 8.0 Hz, 1 H), 6.96 (d, J = 2.4 Hz, 1 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 14.10 (CH_3), 20.38, 29.40 (CH_2), 50.50 (NCH_2), 55.35 (OCH_3), 83.00 (q, J = 29.6 Hz, C-OH), 103.50 (CH=), 111.20 (C-7), 113.90 (C-5), 117.10 (C-4), 125.11 (q, J = 285 Hz, CF_3), 137.40 (C-9), 139.20 (C-8), 151.60 (=C-N), 155.66 (C_{ar}-O) ppm. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = –77.99 ppm. ^{15}N NMR (40.55 MHz, $CDCl_3$): δ = –304.5 ppm.

2-(Diethylamino)-4,7-dimethoxy-1-(trifluoromethyl)-1*H*-inden-1-ol (4d): Yield 47%. Oil. IR (KBr): $\tilde{\nu}$ = 1680 (C=C), 3510 (OH) cm^{-1}. ^1H NMR (400.16 MHz, $CDCl_3$): δ = 1.16 (t, J = 7.0 Hz, 6 H), 3.15–3.30 (m, 2 H), 3.50–3.65 (m, 2 H), 3.82 (s, 3 H), 3.86 (s, 3 H), 4.43 (br. s, 1 H), 5.45 (s, 1 H), 6.46 (d, J = 8.8 Hz, 1 H), 6.76 (d, J = 8.8 Hz, 1 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 12.45 (CH_3), 44.66 (NCH_2), 55.92, 56.32 (OCH_3), 85.53 (q, J = 30.0 Hz, C-OH), 99.11 (CH=), 105.94, 114.26, 122.33 (CH aryl), 125.30 (q, J = 289 Hz, CF_3), 135.16, 145.57, 150.16 (C aryl), 151.95 (=C-N) ppm. $C_{16}H_{20}F_3NO_3$ (331.34): calcd. C 58.00, H 6.08, N 4.23; found C 57.79, H 6.09, N 4.09.

2-(Dipropylamino)-4,7-dimethoxy-1-(trifluoromethyl)-1*H*-inden-1-ol (4e): Yield 74%. Oil. IR (KBr): $\tilde{\nu}$ = 1667 (C=C), 3500 (OH) cm^{-1}. ^1H NMR (400.16 MHz, CD_3CN): δ = 0.85 (t, J = 7.3 Hz, 6 H), 1.45–1.60 (m, 4 H), 2.90–3.05 (m, 2 H), 3.45–3.55 (m, 2 H), 3.73 (s, 3 H), 3.77 (s, 3 H), 4.69 (br. s, 1 H), 5.33 (s, 1 H), 6.50 (d, J = 8.9 Hz, 1 H), 6.79 (d, J = 8.9 Hz, 1 H) ppm. ^{13}C NMR (100.61 MHz, CD_3CN): δ = 11.66 (CH_3), 21.10 (CH_2), 53.29 (NCH_2), 56.34, 56.66 (OCH_3), 86.21 (q, J = 30.0 Hz, C-OH), 99.35 (CH=), 107.17, 115.34, 122.57 (CH aryl), 124.71 (q, J = 289 Hz, CF_3), 135.71, 146.21, 151.30 (C aryl), 153.44 (=C-N) ppm. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = –77.97 ppm. MS (EI): *m*/*z* (%) = 359 (81) $[M]^+$, 330 (100), 270 (28), 248 (29), 218 (17). $C_{18}H_{24}F_3NO_3$ (359.39): calcd. C 60.16, H 6.73, N 3.90; found C 60.26, H 7.21, N 4.01.

2-(Dibutylamino)-4,7-dimethoxy-1-(trifluoromethyl)-1*H*-inden-1-ol (4f): Yield 36%. Solid, m.p. 56–57 °C. IR (KBr): $\tilde{\nu}$ = 1680 (C=C), 3510 (OH) cm^{-1}. ^1H NMR (400.16 MHz, $CDCl_3$): δ = 0.93 (t, J = 7.5 Hz, 6 H), 1.27–1.40 (m, 4 H), 1.50–1.65 (m, 4 H), 2.95–3.10 (m, 2 H), 3.50–3.65 (m, 2 H), 3.80 (s, 3 H), 3.83 (s, 3 H), 4.42 (br. s, 1 H), 5.40 (s, 1 H), 6.44 (d, J = 8.9 Hz, 1 H), 6.74 (d, J = 8.9 Hz, 1 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 14.11 (CH_3), 20.38, 29.50 (CH_2), 50.92 (NCH_2), 55.88, 56.28 (OCH_3), 85.53 (q, J = 30.0 Hz, C-OH), 98.93 (CH=), 105.80, 114.15, 122.20 (CH, aryl),

125.39 (q, J = 289 Hz, CF_3), 132.22, 145.56, 150.17 (C aryl), 152.40 (=C-N) ppm. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = –77.99 ppm. MS (EI): m/z (%) = 387 (100) $[M]^+$, 344 (58), 302 (65), 270 (18), 218 (15). $C_{20}H_{28}F_3NO_3$ (387.45): calcd. C 62.00, H 7.28, N 3.62; found C 61.80, H 7.31, N 3.55.

3-(Dipropylamino)-1,1,1-trifluoro-4-(2-thienyl)-3-buten-2-one (5a): Yield 20%. Oil. IR (KBr): $\tilde{\nu}$ = 1595 (C=C), 1682 (C=O) cm^{-1}. ^1H NMR (400.16 MHz, $CDCl_3$): δ = 0.83 (t, J = 7.5 Hz, 6 H), 1.45–1.55 (m, 4 H), 2.90–3.05 (m, 4 H), 7.11 (dd, J = 5.2, 3.8 Hz, 1 H), 7.45 (d, J = 3.8 Hz, 1 H), 7.59 (d, J = 5.2 Hz, 1 H), 7.74 (s, 1 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 12.08 (CH_3), 21.27 (CH_2), 55.41 (NCH_2), 116.72 (q, J = 293 Hz, CF_3), 126.92 (C-4), 134.44 (C-5), 135.43 (C-3), 136.60 (=C-N), 136.80 (C-2), 138.76 (q, J = 4 Hz, CH=), 179.39 (q, J = 32.5, ^3J = 3.7 Hz, C=O) ppm. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = –69.99 ppm. MS (EI): m/z (%) = 305 (83) $[M]^+$, 276 (100), 179 (22), 123 (27). $C_{14}H_{18}F_3NOS$ (305.36): calcd. C 55.07, H 5.94, N 4.59; found C 55.29, H 6.01, N 4.39.

3-(Dibutylamino)-1,1,1-trifluoro-4-(2-thienyl)-3-buten-2-one (5b): Yield 23%. Oil. IR (KBr): $\tilde{\nu}$ = 1590 (C=C), 1683 (C=O) cm^{-1}. ^1H NMR (400.16 MHz, $CDCl_3$): δ = 0.83 (t, J = 7.0 Hz, 6 H), 1.15–1.25 (m, 4 H), 1.35–1.45 (m, 4 H), 2.90–2.98 (m, 4 H), 7.09 (dd, J = 5.1, 3.9 Hz, 1 H), 7.42 (d, J = 3.9 Hz, 1 H), 7.56 (d, J = 5.1 Hz, 1 H), 7.71 (s, 1 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 14.15 (CH_3), 20.95, 30.16 (CH_2), 53.28 (NCH_2), 116.77 (q, J = 293 Hz, CF_3), 126.91 (C-4), 134.41 (C-5), 135.35 (C-3), 136.82 (=C-N), 136.93 (C-2), 138.63 (q, J = 4.0 Hz, CH=), 179.46 (q, J = 33.0, ^3J = 3.7 Hz, C=O) ppm. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = –70.00 ppm. MS (EI): m/z (%) = 333 (57) $[M]^+$, 290 (100). $C_{16}H_{22}F_3NOS$ (333.42): calcd. C 57.64, H 6.65, N 4.20, S 9.62; found C 57.19, H 6.40, N 4.14, S 9.16.

3-(Dibutylamino)-1,1,1-trifluoro-4-(4-methoxyphenyl)-3-buten-2-one (6a): ^1H NMR (400.16 MHz, $CDCl_3$): δ = 0.93 (t, J = 7.0 Hz, 6 H), 1.25–1.35 (m, 4 H), 1.45–1.55 (m, 4 H), 2.90–2.98 (m, 4 H), 3.74 (s, 3 H), 5.89 (s, 1 H), 6.70–6.80 (m, 2 H), 6.90–7.05 (m, 2 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 13.85 (CH_3), 20.30, 28.50 (CH_2), 50.30 (NCH_2), 55.10 (CH_3O), 114.30 (C-3,5), 115.00 (q, J = 294 Hz, CF_3), 115.80 (CH=), 129.00 (C-2,6), 141.10 (C-1), 158.50 (=C-N), 158.8 (C_{ar}-O), 186.90 (qd, J = 10.3, 34.5 Hz, C=O) ppm. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = –75.00 ppm. ^{15}N NMR (40.55 MHz, $CDCl_3$): δ = –314.00 ($^3J_{H-N}$ = 1.5 Hz) ppm.

4-(2,5-Dimethoxyphenyl)-3-(dipropylamino)-1,1,1-trifluoro-3-buten-2-one (6b): ^1H NMR (400.16 MHz, $CDCl_3$): δ = 0.87 (t, J = 7.2 Hz, 6 H), 150–1.60 (m, 4 H), 2.85–2.95 (m, 4 H), 3.70 (s, 6 H), 5.87 (s, 1 H), 6.70–6.80 (m, 2 H), 6.68 (s, 1 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 11.75 (CH_3), 20.25 (CH_2), 53.48 (NCH_2), 56.25, 56.86 (OCH_3), 112.56, 113.66, 113.81 (CH aryl), 120.86 (C aryl), 125.30 (q, J = 282.0 Hz, CF_3), 116.40 (CH=), 144.10 (=C-N), 150.95, 154.69 (C_{ar}-O), 186.56 (q, J = 34.4 Hz, C=O) ppm. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = –74.67 ppm.

1-Hydroxy-6-methoxy-1-(trifluoromethyl)-1,3-dihydro-2*H*-indan-2-one (8): A mixture of bromoketone **3b** (386 mg, 1.25 mmol) and dibutylamine (330 mg, 2.5 mmol) in diethyl ether (10 mL) was stirred at room temperature for 24 h. The solvent was removed, and water (0.2 mL) and two drops of HCl (conc.) were added to the residue. After 2 h stirring, ether (10 mL) was added. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layer was dried with $MgSO_4$. The solvent was removed, and the residue was purified by column chromatography (silica gel, ether/hexane, 2:1) to give **8** (145 mg, 47%) as white solid. M.p. 153–154 °C. The same reaction with diethylamine as nucleophile afforded indanone **8** in 68% yield. IR (KBr): $\tilde{\nu}$ = 1767 (C=O), 3405 (O-H) cm^{-1}. ^1H NMR (400.16 MHz, $CDCl_3$): δ = 3.46 (A part of AB system, J = 21.5 Hz, 1 H), 3.72 (B part of AB system, J = 21.5 Hz, 1 H), 3.80 (s, 3 H), 6.96 (d, J = 8.3 Hz, 1 H), 7.05 (s, 1 H), 7.21 (d, J = 8.3 Hz, 1 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 40.85 (CH_2), 55.63 (CH_3O), 79.47 (q, J = 30 Hz, C-OH), 110.42 (C-7), 119.01 (C-5), 123.33 (q, J = 286 Hz, CF_3), 126.15 (C-4), 129.07 (C-9), 135.76 (C-8), 160.07 (C-OMe), 207.80 (C=O) ppm. ^{19}F NMR (376.5 MHz, $CDCl_3$): δ = –78.55 ppm. MS (EI): m/z (%) = 246 (40) $[M]^+$, 218 (63), 149 (100), 121 (48). $C_{11}H_9F_3O_3$ (246.19): calcd. C 53.67, H 3.68; found C 53.64, H 3.72.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra of compounds **3a**,**c**,**d**, **4e**,**f**, **5a**, and **8** and 2D NMR for ketone **3c** and indenol **4e**.

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