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Regioselective Carbon−Carbon Bond Formation of 2,2,2−Trifluoroethyl Substituted Tertiary Amines Initiated by Electron Transfer to Photochemically Excited Enone

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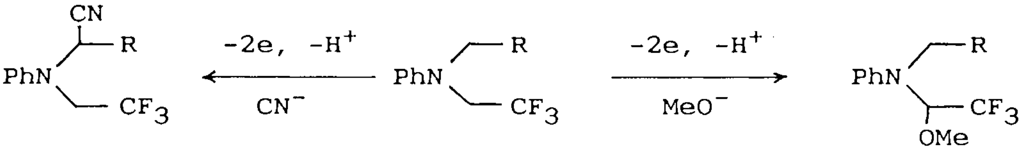
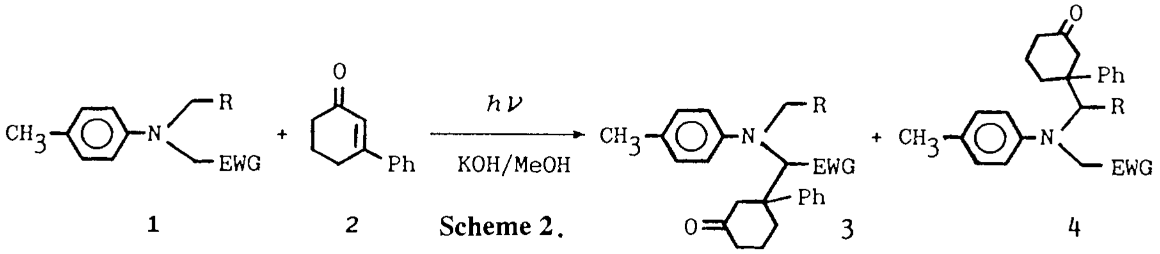
Photoadditions of N−(2,2,2−trifluoroethyl)amines to 3−phenylcyclohex−2−en−1−one occurred at the *α*−position to the trifluoromethyl group predominantly. The regioselectivity of this photoaddition reaction was comparable to that of anodic methoxylation of N−(2,2,2−trifluoroethyl)anilines; this reaction is the first example of direct carbon substitution at *α* to the trifluoromethyl group and this promotion effect was general for other electron−withdrawing groups.

Fluoroorganics have attracted much interest because of their potential biological activity and unique functional properties.1) Their syntheses, however, have many limitations due to strong electronegativity of a fluorine atom. For example, nucleophilic substitution reaction at *α* to the trifluoromethyl group has been hard to occur.2) Although numerous building blocks containing a trifluoromethyl group have been developed,3) their synthesis is not always straightforward. We have recently found that an electron−withdrawing group, especially trifluoromethyl group, promotes the anodic nucleophilic substitution reaction of amines at their *α*−position (Scheme 1).4) Then, we tried anodic cyanation of those amines to accomplish direct carbon−carbon bond formation at *α* to the trifluoromethyl group. However, our attempts were unsuccessful and the cyano group was not introduced to the desired position. We have found that the regiochemistry of anodic cyanation dramatically changed as shown in Scheme 1.5)



Scheme 1.

On the other hand, the oxidation of tertiary amines has been investigated, from both synthetic and mechanistic points of view, by chemical,6) electrochemical,7) photochemical,8) and enzymatical9) oxidation. Among these methods, photochemical oxidation seems to be promissing for direct carbon−carbon bond formation. Although photooxidative addition of non−fluorinated amines to enones is known,10) no paper has been reported on photochemical reactions of fluorinated amines. We therefore attempted photochemical addition of 2,2,2−trifluoroethyl amines to enones in order to investigate (i) the possibility of the direct carbon−carbon bond formation at *α* to the trifluoromethyl group and (ii) the regiochemistry of the photoaddition reactions.



Scheme 2.

Table 1. Photoaddition of anilines (1) to 3-phenylcyclohexenone (2)[a)]

Run	Anilines (1) R	EWG	Irradiation time/h	Conversion[b)] %	Yield/%[c)] 3[d)]	4
1	H	CF_3 (**1a**)	1.0	74	31	14
2	CH_3	CF_3 (**1b**)	2.0	79	56	0
3	H	CN (**1c**)	2.0	61	25	0
4	H	COOMe (**1d**)	2.0	82	14	0

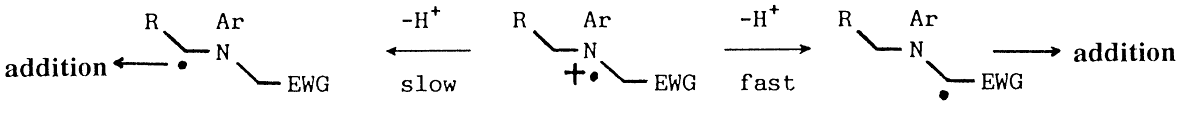
a) Photochemical reaction was conducted in 10 mdm^3 of 0.06 mol/dm^3 solutions of KOH/MeOH with **1** (0.06 mol/dm^3) and **2** (0.06 mol/dm^3). b) Conversion of **1** determined by HPLC. c) Determined by HPLC or ^{19}F NMR (C_6H_5F as an internal standard) based on consumed **1**. d) Mixture of diastereomers.

We chose N-(2,2,2-trifluoroethyl)-p-toluidine derivatives **1a** and **1b** as the model amines in order to avoid oxidative dimerization at the aromatic ring. The advantage of using β-phenylcyclohexenone as an enone is that it has long triplet life time and it is hard to dimerize photochemically compared to simple cyclohexenone.[11,12)]

The methanol solution of an amine (0.06 mol/dm^3) and enone (0.06 mol/dm^3) containing KOH (0.06 mol/dm^3) in a Pyrex test tube under a nitrogen atmosphere was irradiated by a 100-W high pressure mercury lamp. Photoadducts were isolated by preparative thin layer chromatography and characterized by spectroscopic methods.[13)] In some cases, a pair of diastereomers (the amount was almost same each other) could be separated. Yields of photoproducts were determined by HPLC or ^{19}F NMR. The results are summarized in Table 1. The photoadducts were formed in reasonable yields and the reaction took place preferably at α to the trifluoromethyl group of **1a**. In the case of N-ethyl-N-(2,2,2-trifluoroethyl)-p-toluidine (**1b**), photoaddition occurred at α to the trifluoromethyl group exclusively (run 2). To the best of our knowledge, this is the first successful example of direct carbon substitution of the hydrogen atom at α to the trifluoromethyl group. The regiochemistry shown here are quite similar to that of anodic methoxylation reaction of trifluoroethylated aniline derivatives.[4,14)]

Next, we extended this photoaddition to aniline derivatives bearing electron-withdrawing groups other than trifluoromethyl group (runs 3 and 4). The photoaddition reaction also occurred at α to the electron-withdrawing groups (CN and COOMe). On the contrary, aniline derivatives devoid of an electron-withdrawing group did not undergo such photochemical addition at all.

The mechanism of photoaddition of amine-enone system has been investigated intensively so far, and it has been established that the initiation process is electron transfer from amines to excited enones.[10)] The regiochemistry observed here should be controlled by the deprotonation step as shown in Scheme 3. The fact that substitution at α to the electron-withdrawing groups was predominant could be explained by considering kinetic acidity controlled addition as depicted in Scheme 3.[8,15)]



Scheme 3.

In summary, we have shown a new strategy for direct formation of a carbon-carbon bond at α to the trifluoromethyl group.

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12) Indeed, photochemical reaction of cyclohexenone with the amines gave considerable amount of enone [2+2] dimers.

13) ^{1}H NMR spectra were recorded at 270 MHz on JEOL GX-270 NMR spectrometer. The chemical shifts for ^{1}H NMR are given in δ ppm downfield from Me$_4$Si. Spectroscopic data of selected compounds are as follows. **3-{1-[N-Methyl-N-(p-tolyl)amino]-2,2,2-trifluoroethyl}-3-phenylcyclohexan-1-one (3a**: diastereomeric mixture) : ^{1}H NMR (CDCl$_3$) δ 1.25-1.59 (m, 2H), 1.75-1.91 (m, 2H), 2.12-2.29 (m, 6H), 2.23 (s, 3H, $ArC\underline{H}_3$), 2.27 (s, 3H, $ArC\underline{H}_3$), 2.51-2.58 (m, 1H), 2.57 (s, 3H, $N\text{-}C\underline{H}_3$), 2.69-2.75 (m, 1H), 2.76 (d, J = 14.5 Hz, 1H)), 2.85 (d, J = 14.2 Hz, 1H), 2.86 (s, 3H, $N\text{-}C\underline{H}_3$), 3.42 (broad d, J =14.5 Hz, 1H), 3.42 (broad d, J =14.2 Hz, 1H), 4.44 (q, J = 9.2 Hz, 1H, $C\underline{H}CF_3$), 4.55 (q, J = 8.9 Hz, 1H, $C\underline{H}CF_3$), 6.53 (pseudo d, J = 8.6 Hz, 2H), 6.76 (pseudo d, J = 8.6 Hz, 2H), 6.96 (pseudo d, J = 8.6 Hz, 2H), 7.07 (pseudo d, J = 8.6 Hz, 2H), 7.17-7.43 (m, 10H); HRMS Found 375.1762, Calcd for $C_{22}H_{24}F_3NO$: 375.1808. **3-{[N-(p-tolyl)-N-(2,2,2-trifluoroethyl)amino]methyl}-3-phenylcyclohexan-1-one (4a)** : ^{1}H NMR (CDCl$_3$) δ 1.33-1.51 (m, 1H), 1.79 (ddd, J = 17.9, 9.1, 4.2 Hz, 1H), 1.92 (ddd, J = 13.5, 13.0, 3.3 Hz, 1H), 2.13-2.33 (m, 3H), 2.26 (s, 3H, $ArC\underline{H}_3$), 2.51 (d, J = 14.3 Hz, 1H), 2.93 (dd, J = 14.3, 2.3 Hz, 1H), 3.29 (dq, J =17.0, 8.5 Hz, 1H, $C\underline{H}_aH_bCF_3$), 3.35 (dq, J =17.0, 8.5 Hz, 1H, $CH_a\underline{H}_bCF_3$), 3.58 (d, J = 15.4 Hz, 1H, $NC\underline{H}_aH_bCPh$), 3.64 (d, J = 15.4 Hz, 1H, $CH_a\underline{H}_bCPh$), 6.85 (pseudo d, J = 8.6 Hz, 2H), 7.02 (pseudo d, J = 8.6 Hz, 2H), 7.21-7.37 (m, 5H); HRMS Found 375.1780, Calcd for $C_{22}H_{24}F_3NO$: 375.1808. **3-{1-[N-Ethyl-N-(p-tolyl)amino]-2,2,2-trifluoroethyl}-3-phenylcyclohexan-1-one (3b**: diastereomer 1) : ^{1}H NMR (CDCl$_3$) δ 0.92 (dd, J = 7.3, 6.8 Hz, 3H, $CH_2C\underline{H}_3$), 1.44-1.58 (m, 1H), 1.81-1.93 (m, 1H), 2.17-2.34 (m, 3H), 2.22 (s, 3H, $ArC\underline{H}_3$), 2.62 (dd, J = 13.7, 3.0 Hz, 1H), 2.91 (d, J = 14.2 Hz, 1H), 2.99 (dq, J = 14.2, 7.3 Hz, 1H, $C\underline{H}_aH_bCH_3$), 3.24 (dq, J = 14.2, 6.8 Hz, 1H, $CH_a\underline{H}_bCH_3$), 3.40 (broad d, J = 14.2 Hz, 1H), 4.26 (q, J = 9.3 Hz, 1H, $C\underline{H}CF_3$), 6.41 (pseudo d, J = 8.5 Hz, 2H), 6.91 (pseudo d, J = 8.5 Hz, 2H), 7.17-7.42 (m, 5H); HRMS Found 389.1912, Calcd for $C_{23}H_{26}F_3NO$: 389.1964. (**3b**: diastereomer 2) : ^{1}H NMR (CDCl$_3$) δ 1.03 (t, J = 6.8 Hz, 3H, $CH_2C\underline{H}_3$), 1.24-1.41 (m, 1H), 1.75-1.86 (m, 1H), 2.13-2.32 (m, 3H), 2.28 (s, 3H, $ArC\underline{H}_3$), 2.54 (dd, J = 13.9, 3.1 Hz, 1H), 2.68 (d, J = 14.2 Hz, 1H), 3.34 (q, J = 6.8 Hz, 2H, $C\underline{H}_2CH_3$), 3.40 (broad d, J = 14.2 Hz, 1H), 4.40 (q, J = 8.7 Hz, 1H, $C\underline{H}CF_3$), 6.80 (pseudo d, J = 8.3 Hz, 2H), 7.07 (pseudo d, J = 8.3 Hz, 2H), 7.21-7.40 (m, 5H); HRMS Found 389.1931, Calcd for $C_{23}H_{26}F_3NO$: 389.1964.

14) The anodic methoxylation of N-methyl-N-(2,2,2-trifluoroethyl)aniline and N-ethyl-N-(2,2,2-trifluoroethyl)aniline occurred at (trifluoroethyl/alkyl) position in (71/29) and (81/0) %, respectively. See: T. Fuchigami, Y. Fujita, and T. Nonaka, J. Electroanal. Chem., **284**, 115 (1990).

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