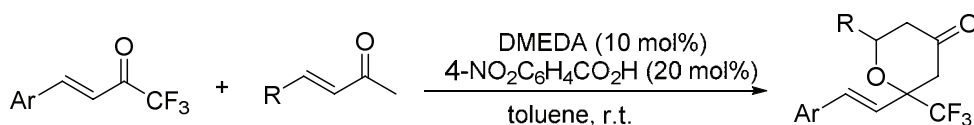


Study on Hetero-Diels-Alder Reactions of α,β -Unsaturated Trifluoromethyl Ketones with Acyclic Aliphatic Ketones

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ABSTRACT Hetero-Diels-Alder (HDA) reaction of α,β -unsaturated trifluoromethyl ketones with acyclic aliphatic ketones has been developed. The effect of acids, the amounts of acid, and solvents on the reaction were investigated, and the optimal condition for the reaction was obtained. In the presence of N,N' -dimethylethylenediamine (10 mol%), *p*-nitrobenzoic acid (20 mol%), and toluene at room temperature as the reaction system, HDA reactions of the different α,β -unsaturated trifluoromethyl ketones with acyclic aliphatic ketones, afforded trifluoromethylated tetrahydropyranone derivatives in high yields (up to 86%). All compounds were characterized by infrared, mass, proton nuclear magnetic resonance, and carbon-13 nuclear magnetic resonance.



KEYWORDS: α,β -Unsaturated trifluoromethyl ketones, Acyclic aliphatic ketones, Hetero-Diels-Alder reactions, Tetrahydropyranone derivatives.

INTRODUCTION

Tetrahydropyran derivatives are intermediates for the synthesis of many pharmaceutical products, and important structural motifs in a plethora of bioactive natural and non-natural products which can be transformed into substituted tetrahydropyran derivatives. The Hetero-Diels-Alder (HDA) reaction is an important method for the construction of six-membered heterocyclic compounds.^[1-4] The dienophiles such as aldehydes, ketones, and imines, can be activated in the presence of the transition metals, Bronsted acids or amines, and then produce six-membered heterocyclic compounds with dienes such as Danishefsky diene, or α,β -unsaturated carbonyl compounds. The Jacobsen group^[5] first reported the tridentate Schiff base chromium complex to catalyze the HDA reaction of Danishefsky diene and aldehyde to produce tetrahydropyran derivatives, and the transition metal and

the small-molecule catalyzed HDA reaction have received much attention in organic synthesis.^[6-9]

At present, the amine-catalyzed HDA reaction has also made great progress.^[10,11] However, when dienes are generated from enones *in situ*, oxa-HDA reactions using carbonyl as dienophiles are very difficult.^[12] As far as we know, the HDA reaction of the carbonyl portion of α,β -unsaturated ketone as dienophile catalyzed by an amine has not been reported. In addition, trifluoromethylated organic compounds, as an important halogen compounds have received increasing attention due to their extensive physicochemical properties compared with other isosteric dehalogenated analogs.^[13] It is believed that the presence of trifluoromethyl groups in pharmaceutical compounds can enhance and modify their pharmacological activities.^[14] Accordingly, an efficient approach that can be used to construct CF₃-bearing organic compound is of considerable synthetic and biological importance.^[15]

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It was found that the enamines generated *in situ* showed a remarkable propensity for the HDA reactions with carbonyl functionality rather than with the electron-deficient double bond. As we are interested in trifluoromethyl group chemistry and aminocatalysis, we reasoned that an amino-butadiene generated *in situ* from primary amine and aliphatic acyclic enone **2** could selectively react with the carbonyl functionality instead of the double bond of α,β -unsaturated enones **1**. Hence, we use α,β -unsaturated trifluoromethyl ketones **1** and acyclic ketone **2** as two reactants to investigate the reaction.

RESULTS AND DISCUSSION

Optimization of reaction conditions

To explore the reaction, we undertook an investigation of *N,N'*-dimethylethylenediamine (10 mol%) and trifluoroacetic acid (20 mol%) for the HDA reaction of α,β -unsaturated trifluoromethyl ketone (**1a**) with 3-hepten-2-one (**2a**) in toluene at room temperature, affording the HDA product **3a** in 12% yield after 72 h [Entry 2, **Table 1**].

To optimize the reaction conditions, this model reaction was chosen for a survey of different acids and solvents. Among these, the reaction cannot happen without acid [Entry 1, **Table 1**]. 4-Nitrobenzoic acid proved to be the best choice, providing HDA product **3a** in 75% yield [Entry 4, **Table 1**]. Generally speaking, the amount of acid had an effect on the yield of the reaction, but this reaction had little effect [Entries 12 and 13, **Table 1**]. In addition, we also investigated the effect of solvents on the yield of the reaction. The results showed that non-polar solvents had obtained relatively good results [Entries 6-8, **Table 1**], and

the reaction results were not identical when the polar aprotic solvent was selected [Entry 9-11, **Table 1**]. Especially, when dimethyl sulfoxide was used as a solvent, the reaction rate was very slow, only 18% yield was obtained [Entry 11, **Table 1**].

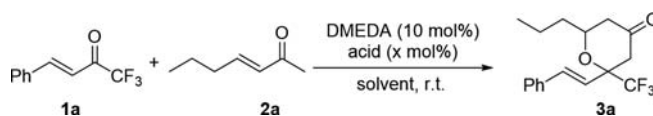
The substrate scope of the reaction

Having established the optimal reaction conditions [Entry 4, **Table 1**], the scope of substrates was then extensively investigated, and the results are summarized in **Table 2**.

All α,β -unsaturated trifluoromethyl ketones reacted with enone **2** to afford the desired HDA products **3a-h** [Entries 1–8, **Table 2**]. It was found that the electronic nature of substituents on the phenyl ring had a significant effect on the reaction. Electron-withdrawing groups were beneficial for affording higher yield [Entries 2, 4, 5 and 7, **Table 2**]. In particular, the yield of 4-bromo substituent was up to 84% [Entry 4, **Table 2**]. In contrast, the yield of electron-donating groups such as methyl or methoxy groups on the phenyl ring was lower [Entries 3 and 6, **Table 2**]. The substrates with larger steric hindrance on the phenyl ring such as naphthyl also proceeded smoothly in the HDA reaction [Entry 8, **Table 2**]. Besides, the other acyclic aliphatic enone was also tested. Acyclic ketone **2** when R is isopropyl reacted with α,β -unsaturated enones **1**, providing the corresponding HDA products **3i-m** in 75–86% yield [Entries 9-13, **Table 2**].

Based on the above results, we hypothesized the possible mechanism of the HDA reaction. In the ammonia catalytic reaction, the nucleophilic alkenamine first attacked the carbonyl group of α,β -unsaturated enones **1** and generated β -hydroxyl ketone compounds, which were the aldol condensation products. The tetrahydropyran derivatives

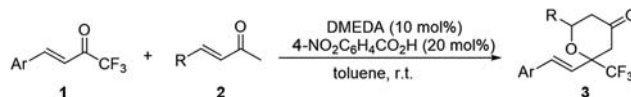
Table 1: Optimization of reaction conditions



Entry ^[a]	Acid	Solvent	Yield/% ^[b]
1	--	Toluene	--
2	TFA	Toluene	12
3	2-FC ₆ H ₄ CO ₂ H	Toluene	50
4	4-NO ₂ C ₆ H ₄ CO ₂ H	Toluene	75
5	HOAc	Toluene	43
6	4-NO ₂ C ₆ H ₃ CO ₂ H	Benzene	72
7	4-NO ₂ C ₆ H ₄ CO ₂ H	DCM	70
8	4-NO ₂ C ₆ H ₄ CO ₂ H	CHCl ₃	72
9	4-NO ₂ C ₆ H ₄ CO ₂ H	THF	34
10	4-NO ₂ C ₆ H ₄ CO ₂ H	CH ₃ CN	38
11	4-NO ₂ C ₆ H ₄ CO ₂ H	DMSO	18
12 ^[c]	4-NO ₂ C ₆ H ₄ CO ₂ H	Toluene	64
13 ^[d]	4-NO ₂ C ₆ H ₄ CO ₂ H	Toluene	73

^[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.5 mmol), *N,N'*-dimethylethylenediamine (10 mol%), acid (20 mol%), toluene (1 mL), room temperature, 48–96 h. ^[b] Yield of isolated product. ^[c] 10 mol% acid used. ^[d] 30 mol% acid used. DMSO: Dimethyl sulfoxide

Table 2: Scope of the substrates on the reaction



Entry ^[a]	Product	Ar	R	Yield/% ^[b]
1	3a	Ph	<i>n</i> -Pr	75
2	3b	4-FC ₆ H ₄	<i>n</i> -Pr	70
3	3c	4-CH ₃ C ₆ H ₄	<i>n</i> -Pr	60
4	3d	4-BrC ₆ H ₄	<i>n</i> -Pr	84
5	3e	3-ClC ₆ H ₄	<i>n</i> -Pr	81
6	3f	3-OMeC ₆ H ₄	<i>n</i> -Pr	64
7	3g	2-BrC ₆ H ₄	<i>n</i> -Pr	72
8	3h	2-Naphthyl	<i>n</i> -Pr	74
9	3i	Ph	<i>i</i> -Pr	75
10	3j	4-FC ₆ H ₄	<i>i</i> -Pr	86
11	3k	4-BrC ₆ H ₄	<i>i</i> -Pr	82
12	3l	3-ClC ₆ H ₄	<i>i</i> -Pr	80
13	3m	2-BrC ₆ H ₄	<i>i</i> -Pr	75

^[a] The reaction was performed on 0.1 mmol scale with **1** (0.1 mmol), **2** (0.5 mmol), N,N'-dimethylethylenediamine (10 mol%), *p*-nitrobenzoic acid (20 mol%) and toluene (1 mL) at room temperature for 48–96 h. ^[b] Yield of isolated product.

observed in the experiment were further synthesized by oxygen conjugation addition reaction.

EXPERIMENTAL

General

Chemicals and solvents were purchased from commercial suppliers or purified by standard techniques. Proton nuclear magnetic resonance (¹H NMR) spectra and carbon-13 nuclear magnetic resonance (¹³C NMR) spectra were recorded in CDCl₃ on an AVANCE III HD spectrometer (Bruker, Germany) operating at 400 and 100 MHz, respectively. Chemical shifts are reported in parts per million relatives to the appropriate standard: Tetramethylsilane for ¹H and ¹³C NMR spectra. Coupling constants (*J*) are reported in Hz and refer to apparent peak multiplications. Flash column chromatography was performed using 200–300 mesh silica gel. Mass spectrometry was carried out by BioTOF Q mass spectrometer (Bruker, Germany).

General procedure for the HDA reaction

To a solution of *p*-nitrobenzoic acid (0.02 mmol) and N,N'-dimethylethylenediamine (0.01 mmol) in toluene (1 mL) were added α,β -unsaturated trifluoromethyl ketones **1** (0.1 mmol) and acyclic aliphatic ketones **2** (0.5 mmol) at room temperature. The reaction mixture was stirred at room temperature until the reaction was complete (monitored by thin-layer chromatography). After removal of the solvent under reduced pressure, the residue was purified through flash column chromatography on silica gel (petroleum ether/ethyl acetate = 150:1–25:1) to afford trifluoromethylated tetrahydropyranone products **3**.

6-Propyl-2-styryl-2-(trifluoromethyl)tetrahydro-4H-pyran-4-one (**3a**)

Yield: 75%, colorless oil. ¹H NMR (CDCl₃, 400MHz), δ : 7.44–7.41 (m, 2H), 7.38–7.29 (m, 3H), 6.91 (d, *J* = 15.9 Hz, 1H), 6.15 (d, *J* = 15.9 Hz, 1H), 4.41–4.36 (m, 1H), 3.06 (d, *J* = 15.5 Hz, 1H), 2.66 (d, *J* = 15.6 Hz, 1H), 2.52 (dd, *J* = 17.1 Hz, 2.8 Hz, 1H), 2.32 (dd, *J* = 17.0 Hz, 11.6 Hz, 1H), 1.84–1.72 (m, 1H), 1.66–1.44 (m, 3H), 1.02 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 100MHz), δ : 203.6, 135.4, 133.4, 128.7, 128.6, 127.0, 125.1 (q, *J* = 288.5 Hz), 124.9, 77.8 (q, *J* = 28.6 Hz), 73.1, 46.0, 43.1, 38.2, 18.3, 13.8; IR (KBr), ν , cm⁻¹: 3094, 3066, 2969, 2923, 2875, 1738, 1601, 1410, 1358, 1250, 1125, 965, 701; ESI-HRMS: Calcd for C₁₇H₂₀F₃O₂ {[M+H]⁺} 313.1410, found 313.1408.

2-(4-Fluorostyryl)-6-propyl-2-(trifluoromethyl)tetrahydro-4H-pyran-4-one (**3b**)

Yield: 70%, colorless oil. ¹H NMR (CDCl₃, 400MHz), δ : 7.39 (d, *J* = 1.3 Hz, 1H), 6.72 (d, *J* = 15.6 Hz, 1H), 6.41 (m, 2H), 6.10 (d, *J* = 15.7 Hz, 1H), 4.39–4.34 (m, 1H), 3.04 (d, *J* = 15.5 Hz, 1H), 2.60 (d, *J* = 15.6 Hz, 1H), 2.50 (dd, *J* = 17.1 Hz, 2.7 Hz, 1H), 2.29 (dd, *J* = 17.0 Hz, 11.6 Hz, 1H), 1.79–1.72 (m, 1H), 1.64–1.42 (m, 3H), 1.01 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 100MHz), δ : 203.5, 164.1, 161.6, 132.2, 131.6 (d, *J* = 3.2 Hz), 128.7, 128.6, 125.1 (q, *J* = 288.6 Hz), 124.7, 115.7, 115.5, 77.7 (q, *J* = 28.7 Hz), 73.1, 46.0, 43.1, 38.1, 18.3, 13.8; IR (KBr), ν , cm⁻¹: 3034, 2912, 2878, 1698, 1585, 1438, 1353, 1215, 1110, 943, 811, 722, 651; ESI-HRMS: Calcd. for C₁₇H₁₉F₄O₂ {[M+H]⁺} 331.1316, found 331.1319.

2-(4-Methylstyryl)-6-propyl-2-(trifluoromethyl)tetrahydro-4H-pyran-4-one (**3c**)

Yield: 60%, colorless oil. ¹H NMR (CDCl₃, 400MHz), δ : 7.31 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 6.86



(d, $J = 15.9$ Hz, 1H), 6.10 (d, $J = 15.9$ Hz, 1H), 4.40–4.35 (m, 1H), 3.05 (d, $J = 15.6$ Hz, 1H), 2.65 (d, $J = 15.6$ Hz, 1H), 2.51 (dd, $J = 17.0$ Hz, 2.8 Hz, 1H), 2.37 (s, 3H), 2.31 (dd, $J = 17.1$ Hz, 11.7 Hz, 1H), 1.81–1.74 (m, 1H), 1.61–1.48 (m, 3H), 1.02 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100MHz), δ : 203.7, 138.6, 133.2, 132.6, 129.3, 126.9, 125.2 (q, $J = 288.3$ Hz), 123.9, 77.8 (q, $J = 28.5$ Hz), 73.0, 46.0, 43.2, 38.2, 21.2, 18.4, 13.8; IR (KBr), ν , cm^{-1} : 3027, 2968, 2805, 1687, 1636, 1520, 1428, 1257, 982, 943, 873, 739, 684; ESI-HRMS: Calcd for $\text{C}_{18}\text{H}_{22}\text{F}_3\text{O}_2\{[\text{M}+\text{H}]^+\}$ 327.1566, found 3391.0569.

2-(4-Bromostyryl)-6-propyl-2-(trifluoromethyl)tetrahydro-4H-pyran-4-one (3d)

Yield: 84%, colorless oil. ^1H NMR (CDCl_3 , 400MHz), δ : 7.51–7.54 (m, 2H), 7.30–7.26 (m, 2H), 6.85 (d, $J = 15.9$ Hz, 1H), 6.14 (d, $J = 15.9$ Hz, 1H), 4.40–4.36 (m, 1H), 3.05 (d, $J = 15.5$ Hz, 1H), 2.63 (d, $J = 15.5$ Hz, 1H), 2.52 (dd, $J = 17.1$ Hz, 2.7 Hz, 1H), 2.30 (dd, $J = 17.0$ Hz, 11.6 Hz, 1H), 1.83–1.70 (m, 1H), 1.64–1.44 (m, 3H), 1.01 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100MHz), δ : 203.3, 134.4, 132.2, 131.8, 128.5, 125.7, 125.0 (q, $J = 288.5$ Hz), 77.7 (q, $J = 28.6$ Hz), 73.1, 46.0, 43.0, 38.1, 18.3, 13.8; IR (KBr), ν , cm^{-1} : 3106, 3013, 2947, 2884, 1716, 1658, 1494, 1403, 1324, 1175, 993, 939, 836, 724, 638; ESI-HRMS: Calcd. for $\text{C}_{17}\text{H}_{19}\text{BrF}_3\text{O}_2\{[\text{M}+\text{H}]^+\}$ 391.0515, found 391.0518.

2-(3-Chlorostyryl)-6-propyl-2-(trifluoromethyl)tetrahydro-4H-pyran-4-one (3e)

Yield: 81%, colorless oil. ^1H NMR (CDCl_3 , 400MHz), δ : 7.41 (s, 1H), 7.30–7.26 (m, 3H), 6.86 (d, $J = 15.8$ Hz, 1H), 6.16 (d, $J = 15.8$ Hz, 1H), 4.41–4.36 (m, 1H), 3.06 (d, $J = 15.5$ Hz, 1H), 2.63 (d, $J = 15.5$ Hz, 1H), 2.52 (dd, $J = 17.1$ Hz, 2.7 Hz, 1H), 2.31 (dd, $J = 17.1$ Hz, 11.6 Hz, 1H), 1.81–1.72 (m, 1H), 1.66–1.47 (m, 3H), 1.02 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100MHz), δ : 203.3, 137.2, 134.7, 132.8, 129.9, 128.5, 126.9, 126.4, 125.2, 125.0 (q, $J = 288.3$ Hz), 77.7 (q, $J = 28.7$ Hz), 73.2, 46.0, 43.1, 38.1, 18.3, 13.8; IR (KBr), ν , cm^{-1} : 3087, 2922, 2834, 1678, 1476, 1398, 1217, 1064, 928, 861, 774, 694; ESI-HRMS: Calcd. for $\text{C}_{17}\text{H}_{19}\text{ClF}_3\text{O}_2\{[\text{M}+\text{H}]^+\}$ 347.1020, found 347.1024.

2-(3-Methoxystyryl)-6-propyl-2-(trifluoromethyl)tetrahydro-4H-pyran-4-one (3f)

Yield: 64%, colorless oil. ^1H NMR (CDCl_3 , 400MHz), δ : 7.30–7.25 (m, 1H), 7.02 (d, $J = 7.7$ Hz, 1H), 6.95–6.93 (m, 1H), 6.89–6.85 (m, 2H), 6.14 (d, $J = 15.8$ Hz, 1H), 4.41–4.32 (m, 1H), 3.85 (s, 3H), 3.06 (d, $J = 15.5$ Hz, 1H), 2.65 (d, $J = 15.6$ Hz, 1H), 2.52 (dd, $J = 17.1$ Hz, 2.7 Hz, 1H), 2.32 (dd, $J = 17.0$ Hz, 11.6 Hz, 1H), 1.81–1.74 (m, 1H), 1.66–1.50 (m, 3H), 1.02 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100MHz), δ : 203.6, 116.0, 136.8, 133.3, 130.0, 125.2, 125.1 (q, $J = 288.4$ Hz), 119.6, 114.3, 112.2, 77.7 (q, $J = 28.7$ Hz), 73.1, 55.3, 46.0, 43.1, 38.2, 18.4, 13.8; IR (KBr), ν , cm^{-1} : 3103, 3046, 2987, 2903, 2824, 1656, 1479, 1388, 1275, 1183, 1007, 984, 901, 787, 712; ESI-HRMS: Calcd for $\text{C}_{18}\text{H}_{22}\text{F}_3\text{O}_3\{[\text{M}+\text{H}]^+\}$ 343.1516, found 343.1517.

2-(2-Bromostyryl)-6-propyl-2-(trifluoromethyl)tetrahydro-4H-pyran-4-one (3g)

Yield: 72%, colorless oil. ^1H NMR (CDCl_3 , 400MHz), δ : 7.61–7.57 (m, 1H), 7.51–7.47 (m, 1H), 7.35–7.29 (m, 2H),

7.19–7.29 (m, 1H), 6.08 (d, $J = 15.8$ Hz, 1H), 4.42–4.38 (m, 1H), 3.08 (d, $J = 15.6$ Hz, 1H), 2.66 (d, $J = 15.6$ Hz, 1H), 2.53 (dd, $J = 17.3$ Hz, 2.9 Hz, 1H), 2.38 (dd, $J = 17.3$ Hz, 11.6 Hz, 1H), 1.83–1.74 (m, 1H), 1.67–1.49 (m, 3H), 1.02 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100MHz), δ : 203.5, 135.5, 133.0, 132.9, 129.8, 127.8, 127.6, 127.4, 124.9 (q, $J = 288.2$ Hz), 124.2, 77.4 (q, $J = 28.7$ Hz), 73.1, 45.8, 43.0, 38.1, 18.3, 13.8; IR (KBr), ν , cm^{-1} : 3099, 3015, 2954, 2867, 1689, 1415, 1309, 1236, 1108, 996, 871, 754, 692; ESI-HRMS: Calcd. for $\text{C}_{17}\text{H}_{19}\text{BrF}_3\text{O}_2\{[\text{M}+\text{H}]^+\}$ 391.0515, found 391.0510.

2-(2-(Naphthalen-1-yl)styryl)-6-propyl-2-(trifluoromethyl)tetrahydro-4H-pyran-4-one (3h)

Yield: 74%, yellow oil. ^1H NMR (CDCl_3 , 400MHz), δ : 8.03 (d, $J = 8.3$ Hz, 1H), 7.89–7.83 (m, 2H), 6.70 (d, $J = 15.6$ Hz, 1H), 7.60–7.45 (m, 4H), 6.18 (d, $J = 15.6$ Hz, 1H), 4.47–4.43 (m, 1H), 3.13 (d, $J = 15.5$ Hz, 1H), 2.75 (d, $J = 15.5$ Hz, 1H), 2.57 (dd, $J = 17.1$ Hz, 2.8 Hz, 1H), 2.40 (dd, $J = 17.2$ Hz, 11.6 Hz, 1H), 1.89–1.78 (m, 1H), 1.70–1.50 (m, 3H), 1.05 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100MHz), δ : 203.7, 133.6, 133.4, 131.2, 128.8, 128.6, 128.2, 126.4, 125.5, 125.1 (q, $J = 288.4$ Hz), 124.4, 123.6, 77.6 (q, $J = 28.5$ Hz), 73.2, 46.0, 43.2, 38.2, 18.4, 13.9; IR (KBr), ν , cm^{-1} : 3055, 2991, 2887, 1694, 1478, 1365, 1204, 1017, 938, 825, 755, 713; ESI-HRMS: Calcd. for $\text{C}_{21}\text{H}_{22}\text{F}_3\text{O}_2\{[\text{M}+\text{H}]^+\}$ 363.1566, found 363.1568.

6-Isopropyl-2-styryl-2-(trifluoromethyl)tetrahydro-4H-pyran-4-one (3i)

Yield: 75%, colorless oil. ^1H NMR (CDCl_3 , 400MHz), δ : 7.43–7.40 (m, 2H), 7.38–7.30 (m, 3H), 6.91 (d, $J = 15.9$ Hz, 1H), 6.15 (d, $J = 15.8$ Hz, 1H), 4.13–4.08 (m, 1H), 3.06 (d, $J = 15.5$ Hz, 1H), 2.63 (d, $J = 15.5$ Hz, 1H), 2.52 (dd, $J = 17.0$ Hz, 2.7 Hz, 1H), 2.34 (dd, $J = 17.0$ Hz, 11.8 Hz, 1H), 1.97–1.89 (m, 1H), 1.10 (d, $J = 6.7$ Hz, 3H), 1.03 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100MHz), δ : 204.0, 135.4, 133.3, 128.7, 128.6, 125.1 (q, $J = 288.6$ Hz), 125.0, 78.0, 77.7 (q, $J = 28.7$ Hz), 43.3, 43.0, 33.1, 18.0, 17.9; IR (KBr), ν , cm^{-1} : 3046, 2967, 2895, 2849, 1706, 1497, 1388, 1259, 1176, 1017, 913, 802, 711; ESI-HRMS: Calcd. for $\text{C}_{17}\text{H}_{20}\text{F}_3\text{O}_2\{[\text{M}+\text{H}]^+\}$ 313.1410, found 313.1416.

b2-(4-Fluorostyryl)-6-isopropyl-2-(trifluoromethyl)tetrahydro-4H-pyran-4-one (3j)

Yield: 86%, colorless oil. ^1H NMR (CDCl_3 , 400MHz), δ : 7.41–7.37 (m, 2H), 7.06–7.02 (m, 2H), 6.87 (d, $J = 15.9$ Hz, 1H), 6.07 (d, $J = 15.9$ Hz, 1H), 4.13–4.09 (m, 1H), 3.06 (d, $J = 15.5$ Hz, 1H), 2.63 (d, $J = 15.5$ Hz, 1H), 2.52 (dd, $J = 17.1$ Hz, 2.8 Hz, 1H), 2.34 (dd, $J = 17.1$ Hz, 11.8 Hz, 1H), 1.98–1.86 (m, 1H), 1.10 (d, $J = 6.7$ Hz, 3H), 1.02 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100MHz), δ : 204.0, 162.9 (q, $J = 248.5$ Hz), 132.1, 131.6 (d, $J = 3.2$ Hz), 128.7, 128.6, 125.1 (q, $J = 288.1$ Hz), 124.7, 115.8, 115.5, 78.0, 77.8 (q, $J = 28.6$ Hz), 43.3, 43.0, 33.1, 18.0, 17.9; IR (KBr), ν , cm^{-1} : 3105, 3053, 2981, 2873, 2802, 2779, 1719, 1503, 1423, 1296, 1117, 987, 876, 784, 664; ESI-HRMS: Calcd for $\text{C}_{17}\text{H}_{19}\text{F}_4\text{O}_2\{[\text{M}+\text{H}]^+\}$ 331.1316, found 331.1321.

2-(4-Bromostyryl)-6-isopropyl-2-(trifluoromethyl) tetrahydro-4H-pyran-4-one (3k)

Yield: 82%, colorless oil. ¹H NMR (CDCl₃, 400MHz), δ: 7.51–7.47 (m, 2H), 7.31–7.27 (m, 2H), 6.85 (d, *J* = 15.8 Hz, 1H), 6.14 (d, *J* = 15.8 Hz, 1H), 4.12–4.08 (m, 1H), 3.06 (d, *J* = 15.5 Hz, 1H), 2.62 (d, *J* = 15.5 Hz, 1H), 2.52 (dd, *J* = 17.1 Hz, 2.7 Hz, 1H), 2.33 (dd, *J* = 17.1 Hz, 11.8 Hz, 1H), 1.98–1.86 (m, 1H), 1.10 (d, *J* = 6.7 Hz, 3H), 1.02 (d, *J* = 6.9 Hz, 3H); ¹³C NMR (CDCl₃, 100MHz), δ: 203.9, 134.3, 133.2, 131.8, 128.5, 125.7, 125.0 (q, *J* = 287.3 Hz), 123.6, 122.5, 78.0, 77.8 (q, *J* = 28.7 Hz), 43.3, 43.0, 33.1, 18.0, 17.9; IR (KBr), ν, cm⁻¹: 3094, 2988, 2876, 2799, 1687, 1447, 1325, 1204, 1001, 963, 828, 754, 657; ESI-HRMS: Calcd. for C₁₇H₁₉BrF₃O₂ {[M+H]⁺} 391.0515, found 391.0509.

2-(3-Chlorostyryl)-6-isopropyl-2-(trifluoromethyl) tetrahydro-4H-pyran-4-one (3l)

Yield: 80%, colorless oil. ¹H NMR (CDCl₃, 400MHz), δ: 7.57 (s, 1H), 7.28 (s, 3H), 6.86 (d, *J* = 15.8 Hz, 1H), 6.16 (d, *J* = 15.8 Hz, 1H), 4.13–4.09 (m, 1H), 3.06 (d, *J* = 15.4 Hz, 1H), 2.62 (d, *J* = 15.4 Hz, 1H), 2.52 (dd, *J* = 17.0 Hz, 2.6 Hz, 1H), 2.33 (dd, *J* = 17.0 Hz, 11.8 Hz, 1H), 1.96–1.88 (m, 1H), 1.10 (d, *J* = 6.7 Hz, 3H), 1.02 (d, *J* = 6.9 Hz, 3H); ¹³C NMR (CDCl₃, 100MHz), δ: 203.8, 137.2, 134.7, 132.1, 130.0, 129.3, 128.5, 126.9, 125.2, 125.0 (q, *J* = 288.4 Hz), 78.0, 77.7 (q, *J* = 28.6 Hz), 43.3, 43.0, 33.1, 18.0, 17.9; IR (KBr), ν, cm⁻¹: 3068, 3002, 2922, 2876, 2811, 1645, 1451, 1297, 1175, 976, 908, 816, 721, 636; ESI-HRMS: Calcd. for C₁₇H₁₉ClF₃O₂ {[M+H]⁺} 347.1020, found 347.1016.

2-(2-Bromostyryl)-6-isopropyl-2-(trifluoromethyl) tetrahydro-4H-pyran-4-one (3m)

Yield: 75%, colorless oil. ¹H NMR (CDCl₃, 400MHz), δ: 7.58 (dd, *J* = 8.0 Hz, 1.0 Hz, 1H), 7.50 (dd, *J* = 7.7 Hz, 1.4 Hz, 1H), 7.34 (d, *J* = 15.8 Hz, 1H), 7.29 (d, *J* = 7.7 Hz, 1H), 7.19–7.15 (m, 1H), 6.08 (d, *J* = 15.7 Hz, 1H), 4.17–4.12 (m, 1H), 3.08 (d, *J* = 15.5 Hz, 1H), 2.64 (d, *J* = 15.5 Hz, 1H), 2.52 (dd, *J* = 17.2 Hz, 2.9 Hz, 1H), 2.41 (dd, *J* = 17.1 Hz, 11.6 Hz, 1H), 2.00–1.91 (m, 1H), 1.12 (d, *J* = 6.8 Hz, 3H), 1.06 (d, *J* = 6.9 Hz, 3H); ¹³C NMR (CDCl₃, 100MHz), δ: 203.9, 135.5, 133.0, 132.7, 129.8, 127.7, 127.6, 127.3, 125.0 (q, *J* = 288.5 Hz), 124.3, 77.9, 77.8 (q, *J* = 28.7 Hz), 43.1, 43.0, 33.0, 17.9, 17.8; IR (KBr), ν, cm⁻¹: 3041, 2952, 2886, 2809, 1692, 1476, 1325, 1207, 1047, 988, 864, 787, 625; ESI-HRMS: Calcd. for C₁₇H₁₉BrF₃O₂ {[M+H]⁺} 391.0515, found 391.0523.

CONCLUSION

In summary, we have developed a mild and efficient protocol for N,N'-dimethylethylenediamine-catalyzed HDA reaction. Through the reaction of α,β-unsaturated trifluoromethyl ketones **1** and acyclic aliphatic ketones **2**, we have successfully obtained the corresponding trifluoromethylated tetrahydropyran derivatives in 60–86% yield. Further studies of the detailed reaction mechanism of this process and its application are underway in our laboratory.

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