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A convenient stereoselective synthesis of trifluoromethyl-substituted polyfunctionalized cyclopropane: synthesis of (±)-*trans*-trifluoronorcoronamic acid

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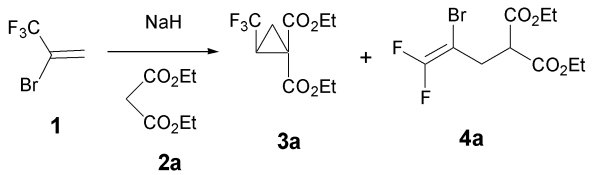
Trifluoromethylated polyfunctionalized cyclopropanes were obtained in high stereoselectivity by reacting 2-bromo-3,3,3-trifluoropropene (BrTFP) with active methylenes. This novel method was further applied to the synthesis of (±)-*trans*-trifluoronorcoronamic acid.

Natural and synthetic cyclopropanes bearing simple functionalities exhibit a wide spectrum of biological properties, ranging from enzyme inhibition to insecticidal, antifungal, herbicidal, antimicrobial, antibiotic, antibacterial, antitumor and antiviral activities.[1] Fluorine or fluorine-containing groups on a cyclopropane ring alter both its chemical reactivity and biological activity due to the strong electron-withdrawing nature of fluorine, and this makes it possible to create new molecules that would exhibit a unique biological activity.[2] Many methods have been reported for the synthesis of cyclopropyl derivatives.[3] However, there are very limited reports on the stereoselective preparation of trifluoromethyl-substituted cyclopropyl derivatives.[4] Several methods, such as photolysis of explosive diazotrifluoroethane[5] or [(trifluoromethyl)azo]cyclopropane,[6] as well as conversion of cyclopropanecarboxylic acid into trifluoromethyl group by SF_4,[7] have been applied for the synthesis of trifluoromethyl-substituted cyclopropanes. However, these methods have some drawbacks, such as the difficulty of obtaining the starting materials, low yields of the products and low stereoselectivities. The development of an efficient and practical method for the synthesis of CF_3-containing cyclopropane in a stereoselective manner is highly desirable. Herein, we report a convenient stereoselective approach for the synthesis of trifluoromethyl-substituted polyfunctionalized cyclopropanes by reacting 2-bromotrifluoropropene (BrTFP, **1**) with active methylenes in a one-pot reaction, and also demonstrate the versatility of this trifluoromethylated synthon by synthesizing (±)-*trans*-trifluoronorcoronamic acid.

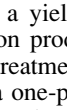
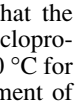
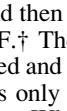
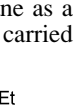
Initially, reacting BrTFP with diethyl malonate **2a** at 50 °C by using NaH (1 equiv.) as base gave a mixture of trifluoromethylated cyclopropane **3a** and defluorination product **4** in a ratio of 18:82 with a yield of 83% (Scheme 1). We found that the defluorination product **4** was easily converted into cyclopropane **3a** by treatment with 2 equiv. of KF in DMF at 110 °C for 4 h. Thus, a one-pot reaction was carried out by treatment of BrTFP with active methylene derivatives **2**/NaH in DMF at 50 °C firstly and then heated at 110 °C for 6 h in the presence of 2 equiv. of KF.† The behavior of a series of active methylenes was examined and the results are summarized in Table 1. All of the reactions only gave trifluoromethylated cyclopropane as a single product. When the cyclopropanation reaction was carried out with diethyl malonate **2a** and malononitrile **2b**, the corresponding cyclopropanes **3a** and **3b** were obtained as the sole product in 82% and 83% yield respectively (entries 1–2). The reaction of methyl phenylsulfonylacetate **2d** and phenylsulfonylacetonitrile **2e** gave cyclopropanes **3c** and **3e** in high yield (entries 3–4). Benzoylacetonitrile **2f** was somewhat sluggish in the cyclopropanation reaction and gave **3f** in moderate yield (entry 5). The stereochemistry of the cyclopropanation products of active methylenes containing two different electron-withdrawing groups was established by comparing the ^{19}F NMR data of **3**[4] with those reported for *cis*-trifluoromethylcyclopropyl cyanide. It was revealed that there was a *cis*-relationship between the trifluoromethyl and cyano group in **3f**, and between the trifluoromethyl and carboxy group in **3d**. The X-ray structure analysis of compound **3e** gave clear evidence of a *cis*-relationship between the C-2 trifluoromethyl group and the C-1 cyano group (Fig. 1).‡

1-Aminocyclopropanecarboxylic acids (ACCs) are of interest because of their outstanding biological activities and potential use in conformationally restricted peptides providing biosynthetic and mechanistic probes.[8] Although there are many published examples of the synthesis of cyclopropyl amino compounds, there have been a few reports on the fluorinated analogues of cyclopropyl amino acids. Having established an efficient method for preparing a series of trifluoromethylated cyclopropanes, we then focused our attention on its practical application to readily available building blocks to obtain synthetic fluorinated analogues of norcoronamic acid.[4] Treating with KOH in ethanol at room temperature, the *trans*-ethyl ester



Scheme 1

Table 1 Reaction of BrTFP (**1**) with active methylene **2**[a]

Entry	2	3	Yield[b]
1	 **2b**	 **3b**	83
2	 **2c**	 **3c**	80
3	 **2d**	 **3d**	91
4	 **2e**	 **3e**	90
5	**2f**	**3f**	60

[a] All reactions were carried out with 1 equiv. BrTFP, 1 equiv. NaH and 2 equiv. KF for 2 h at 50 °C, then at 110 °C for 6 h. [b] Isolated yield.

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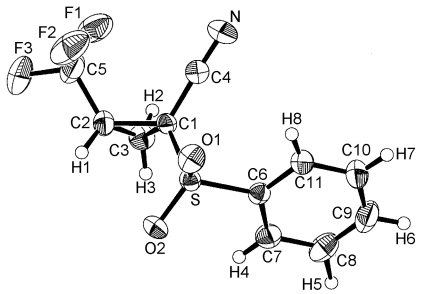
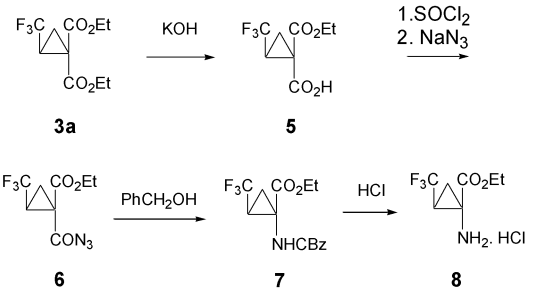


Fig. 1 X-Ray crystallography of compound **3e**.

in **3a** was selectively hydrolyzed to give *trans*-carboxylic acid **5**. The *cis*-ethyl ester in **3a** blocked by a C-2 trifluoromethyl group could not be hydrolyzed. The carboxylic acid **5** was heated with $SOCl_2$ and further reaction with sodium azide in acetone at room temperature produced **6**. Curtius rearrangement of the compound was carried out by heating in a toluene solution of **6** in the presence of benzyl alcohol to give the *N*-Cbz-protected amine **7**.[9] The total yield was 50% in four steps. Finally, heating **7** with 3N HCl afforded (±)-*trans*-trifluoronorcoronamic acid (**8**) hydrochloride salt (Scheme 2).



Scheme 2

In summary, CF_3-substituted polyfunctionalized cyclopropanes were prepared from readily available 2-bromotrifluoropropene in good yield in a one-pot reaction. The salient features of the present protocol are (1) the facile synthesis and high stereoselectivity of CF_3-substituted cyclopropyl derivatives under mild condition and simple manipulation and (2) rapid access to a wide range of functionalized trifluoromethylated substituted cyclopropanes. To demonstrate the utility of these trifluoromethylated building blocks, we transformed compound **3a** to trifluoronorcoronamic acid (**8**).

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Notes and references

† General procedure for the preparation of **3**. To a suspension solution of NaH (5 mmol) and anhydrous KF (580 mg, 10 mmol) in DMF (20 mL) was added **2** (5 mmol) at ambient temperature under nitrogen atmosphere. After 10 min, 2-bromotrifluoropropene (0.5 mL, 6 mmol) was added dropwise at 0 °C for 30 min. The mixture was heated at 50 °C for 2 h and then at 110 °C for 6 h (monitored with ^{19}F NMR). The mixture was poured into ice water and extracted with ethyl acetate. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. Solvent was removed *in vacuo*, and the crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 15 : 1) to afford **3**. All of new compounds give satisfactory analytical and spectral data. Selected spectroscopic data for (**3a**): ^{19}F NMR ($CDCl_3$) δ_{TFA} −13.0 (d, J = 7.5 Hz); ^1H NMR ($CDCl_3$) δ 1.28 (m, 3H), 1.55 (dd, J = 9.1, 5.5 Hz, 1H), 1.80 (dd, J = 7.2, 5.9 Hz, 1H), 2.57 (m, 1H), 4.24 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.8 (s), 14.0 (s), 15.4 (s), 27.0 (q, J = 29.0 Hz), 33.4 (s), 62.2 (s), 62.6 (s), 124.2 (q, J = 212.3 Hz), 165.2 (s), 168.3 (s). (**3b**),:^{19}F NMR ($CDCl_3$) δ_{TFA} −12.5 (d, J = 6. Hz); ^1H NMR ($CDCl_3$) δ 2.21 (m, 2H), 2.89 (m, 1H); (**3c**): ^{19}F NMR ($CDCl_3$) δ_{TFA} −13.0 (d, J = 6.0 Hz); ^1H NMR ($CDCl_3$) δ 1.37 (t, J = 7.1 Hz, 3H), 1.99 (m, 2H), 2.65 (m, 1H), 4.32 (q, J = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.9 (s), 17.2 (d, J = 2.2 Hz), 19.5 (q, J = 2.8 Hz), 29.8 (q, J = 40.7 Hz), 64.1 (s), 122.2 (q, J = 283.6 Hz), 165.3 (s). (**3d**):^{19}F NMR ($CDCl_3$) δ_{TFA} −13.5 (d, J = 6.2 Hz); ^1H NMR ($CDCl_3$) δ 2.07 (dd, J = 7.2, 7.0 Hz, 1H), 2. 17 (m, 1H), 2.70 (m, 1H), 3.69 (s, 3H), 7.60 (m, 2H), 7.71 (m, 1H), 7.89 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.7 (q, J = 2.5 Hz), 27.4 (q, J = 40.9 Hz), 49.2 (s), 53.7 (s), 123.3 (q, J = 284.0 Hz), 129.2 (s), 134.7 (s), 137.7 (s), 162.7 (s). (**3e**): ^{19}F NMR ($CDCl_3$) δ_{TFA} −12.5 (d, J = 7.5 Hz); ^1H NMR ($CDCl_3$) δ 2.05 (dd, J = 7.2, 7.0 Hz, 1H), 2.25 (m, 1H), 2.87 (m, 1H), 7.69 (m, 2H), 7.80 (m, 1H), 8.01 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 16.7 (d, J = 2.4Hz), 27.9(q, J = 41.0 Hz), 122.2 (q, J = 284.6 Hz), 129.2 (s), 130.0 (s), 135.6 (s), 138.8 (s). (**3f**): ^{19}F NMR (CDCl3) δ_{TFA} −12.5 (d, J = 6.5 Hz); ^1H NMR ($CDCl_3$) δ 3.97 (m, 1H), 4.78 (m, 2H), 7.48 (m, 3H), 7.97 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 29.8 (s), 48.6 (q, J = 32.0 Hz), 70.4 (q, J = 2.8 Hz), 115.7 (s), 125.2 (q, J = 290.6 Hz), 126.7 (s), 127.7 (s), 128.9 (s), 132.6 (s), 171.5 (s). (**4a**): ^{19}F NMR ($CDCl_3$) δ_{TFA} 7.0 (d, J = 37.6 Hz, 1F), 11.5 (d, J = 37.6 Hz, 1F); ^1H NMR ($CDCl_3$) δ 1.28 (t, J = 7.1 Hz, 6H), 2.97 (m, 2H), 3.70 (t, J = 7.6 Hz, 1H), 4.22 (dq, J = 1.0, 7.0 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 14.0 (s), 30.4 (s), 50.0 (t, J = 2.7 Hz), 61.9 (s), 77.2 (dd, J = 25.7 Hz), 153.9 (dd, J = 295.6 Hz), 167.9 (s). (**7**): ^{19}F NMR ($CDCl_3$) δ_{TFA} −18.0 (d, J = 6.6 Hz); ^1H NMR ($CDCl_3$) δ 1.19 (t, J = 7.1 Hz, 3H), 1.62 (m, 1H), 2.18 (m, 2H), 4.17(q, J = 7.0 Hz, 2H), 5.12 (s, 2H), 5.75 (s, 1H), 7.30 (m, 5H). (**8**),^{19}F NMR ($CDCl_3$) δ_{TFA} −18.0 (d, J = 9.4 Hz); ^1H NMR (D_2O) δ 1.94 (1H, dd, J = 9.5, 8.1 Hz), 2.23 (1H, t, J = 8.0 Hz), 2.71 (1H, m); ^{13}C NMR (D_2O) δ 18.1 (q, J = 2.5 Hz), 30.4 (q, J = 42.0 Hz), 40.4 (s), 126.2 (q, J = 283.0 Hz), 171.0 (s).

‡ *Crystal data* for **3e**. $C_{11}H_8F_3N\,O_2S$, M = 275.24, monoclinic $C2/c$; a = 22.596(8), b = 5.881(3), c = 20.446(7) Å, V = 2386.7(17) Å^3, α = 90.00, β = 118.55(3), γ = 90.00°, T = 293(2) K, Z = 8, μ(Mo-Kα) = 0.303, CCDC 196988. See http://www.rsc.org/suppdata/cc/b2/b210642f/ for crystallographic files in CIF or other electronic format.

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