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Economical and Practical Strategies for Synthesis of α-Trifluoromethylated Amines

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A powerful approach to synthesize α-trifluoromethylated amines has been developed. The method is operationally simple, broad in substrate scope and amenable to scale-up using trifluoroacetic anhydride. Meanwhile, the strategy not only provided a versatile approach to synthesize α-trifluoromethylated amines but also provides a new method for exploring the new reactivity of trifluoroacetic anhydride.

Keywords: Trifluoromethylated amines, Trifluoroacetic anhydride, α-Trifluoromethylated amines, Grignard reagents.

INTRODUCTION

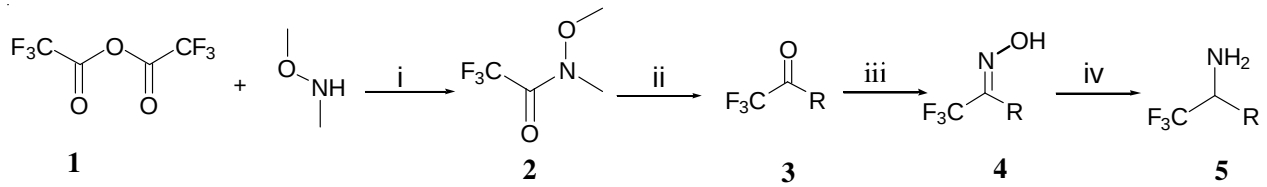
Compounds related to α-trifluoromethylated amines have attracted considerable attention due to the special chemical, physical and biological properties conferred by the introduction of trifluoromethyl group[1-5]. The available synthetic methods for α-trifluoromethylated amines mainly involve the direct transformation of CF_3 with nucleophilic or electrophilic trifluoromethylating reagents and the use of trifluoromethyl-substituent imines[6-9]. However, trifluoromethylating reagents such as $C_6H_5SCF_3$[10], $CF_3CH(NMe_2)_2$[11] and Me_3SiCF_3[12] are often very expensive or difficult to be prepared. And trifluoromethyl-substituent imines are not easily available and unstable. Therefore, the synthetic processes mentioned above are not suitable for large-scale production and industrialization. Here, we wish to describe the economical and practical methods for the preparation of α-trifluoromethylated amines.

As shown in **Scheme-I**, α-trifluoromethylated ketones were the crucial intermediates which were formed by the reaction of Weinreb amide with Grignard reagents. Weinreb amide can be easily synthesized from trifluoroacetic anhydride at room temperature with high yield, which avoided very low reaction temperature (-78 °C) starting from ethyl trifluoroacetate and the separation with the unreacted raw material[13,14].

EXPERIMENTAL

All the reagents and solvents were industrial grade and used without further purification. NMR spectra were recorded on a Bruker Avance DPX-250. The purity of both starting materials as well as the reaction products were checked by TLC on silica-gel polygram SILG/ UV254 plates or by a Shimadzu Gas Chromatograph GC-10A instrument with a flame-ionization detector using a 15 % carbowax 20 M chromosorb-w acid washed 60-80 mesh column.

General procedure: To a suspension of N,O-dimethylhydroxylamine hydrochloride (107.2 Kg, 1.1 kmol) in dichloromethane (400 L) were added trifluoroacetic anhydride (210 Kg, 1 kmol) and pyridine (174 Kg, 2.2 kmol) sequentially at 0 °C. The mixture was stirred at 0°C for 1 h and then diluted with ice water (300 L) and washed with 2 M HCl (300 L). The aqueous solution was extracted twice with dichloromethane and dried under $MgSO_4$. The crude Weinreb amide was obtained after concentration without further purification (90 % purity, 95 % yield). A mixture of the above 2,2,2-trifluoro-N-



Scheme-I: Processes for synthesis of α-trifluoromethylated amines starting from trifluoroacetic anhydride and conditions: (i) CH_2Cl_2, rt, 95 %; (ii) RMgBr, THF, 0 °C, 76-90 %; (iii) $NH_2OH.HCl$, CH_3COONa, rt, 90-99 %; (iv) H_2, Raney nickel, 90 °C, 98 %

methoxy-N-methylacetamide (3 Kg, 90 % purity, 0.017 kmol) in anhydrous THF (30 L) was cooled to 0 °C and treated with 0.5 M Grignard reagent in THF (42 L). The reaction mixture was stirred at 0 °C for 0.5 h and allowed to warm to room temperature. The resulting mixture was stirred at room temperature overnight. The reaction was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate three times. The organic layers were combined and washed with water and brine, dried over $MgSO_4$ and filtered. After rectification, the resulting α-trifluoromethylated ketones were obtained (95 % purity, 90 % yield).

Taking 1,1,1-trifluoro-2-propylamine as an example. Hydroxylamine hydrochloride (3.7 Kg, 53 mol) was added to a solution of sodium acetate (5.3 Kg, 64 mol) in 20 L water. Subsequently, 1,1,1-trifluoroacetone (3 Kg, 26.8 mol) was dosed within 0.5 h at a temperature range of -5 to + 10 °C. The reaction mixture was stirred at room temperature overnight. The crude oxime was diluted with a solution of sodium carbonate (0.7 Kg) in 5 L water and then separated. The low-boiling-point substances were then removed under reduced pressure to yield a pale yellow solid which was used for the next step without further purification. An autoclave was charged with 3 Kg of the oxime obtained above, 0.1 Kg of Raney nickel (moisturized with methanol) and 30 L of methanol. The autoclave was pressurized with hydrogen at a pressure of 0.2 MPa and heated to 90 °C. After hydrogen was consumed completely, the reaction mixture was cooled to room temperature and filtered. The filtrate was cooled down and acidified with diluted hydrochloric acid. The acidified solution was evaporated and the obtained solid was washed with diethyl ether and dried to yield 2-amino-1,1,1-trifluoropropane hydrochloride. Hydrochloride obtained above was placed in a three necked flask with stirrer, dropping funnel and condenser. The oil bath was heated up to 90 °C and an aqueous sodium hydroxide solution was slowly added to the flask. The liberated amine was collected by distillation with a boiling point of 46-47 °C (98 % yield).

NMR data of compound 3 and 5

Compound 3a: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.42 (3H, CH_3, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.66, 115.38, 23.65.

Compound 3b: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.77 (2H, CH_2, m), 1.18 (3H, CH_3, t); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.14, 115.63, 29.87, 6.27.

Compound 3d: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05-7.42 (5H, aromatic protons, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.35, 135.53, 130.11, 129.92, 129.10, 116.68.

Compound 3e: ^{1}H NMR (400 MHz, $CDCl_3$):δ 7.49 (4H, aromatic protons, m), 3.90 (3H, OCH_3, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.30, 159.97, 131.01, 130.07, 122.63, 122.14, 118.10, 113.84, 55.37.

Compound 3f: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (1H, aromatic protons, s), 8.28 (1H, aromatic protons, d), 8.00 (1H, aromatic protons, d), 7.75 (1H, aromatic protons, t); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.53, 133.10, 131.87, 130.46, 129.92, 126.84, 124.54, 121.84, 114.92.

Compound 3g: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90-7.45 (4H, aromatic protons, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.69, 163.97, 131.73, 130.95, 125.94, 122.88, 122.67, 116.60.

Compound 3h: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (2H, aromatic protons, d), 7.55 (2H, aromatic protons, d); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.45, 142.48, 131.42, 129.57, 128.22, 116.52.

Compound 3i: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.09 (5H, aromatic protons, m), 3.94 (2H, CH_2Ph, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.68, 131.26, 130.31, 129.62, 128.93, 127.94, 43.02.

Compound 5a: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.44-3.17 (1H, $CHCF_3$, m), 1.38 (2H, NH_2, s), 1.25 (3H, CH_3, d); ^{13}C NMR (100 MHz, $CDCl_3$): δ 126.83, 49.46, 15.66.

Compound 5b: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.04 (1H, NH, s), 1.77 (1H, $CHCF_3$, m), 1.36 (3H, $NHCH_2$, m), 1.05 (3H, CH_3, t); ^{13}C NMR (100 MHz, $CDCl_3$): δ 126.80, 55.13, 23.02, 10.18.

Compound 5c: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.00 (1H, $CHCF_3$, m), 2.15-1.93 (1H, $CH(CH_3)_2$, m), 1.32 (2H, NH_2, s), 1.06 (3H, CH_3, d), 0.98 (3H, CH_3, d); ^{13}C NMR (100 MHz, $CDCl_3$): δ 126.94, 58.10, 27.79, 20.32, 16.31.

Compound 5d: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (5H, aromatic protons, m), 4.41 (1H, $CHCF_3$, m), 2.05 (2H, NH_2, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.52, 128.95, 128.67, 127.83, 124.34, 57.95.

Compound 5e: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (1H, aromatic protons, t), 6.88 (3H, aromatic protons, m), 6.21 (1H, NH, d), 5.75-5.46 (1H, $CHCF_3$, m), 3.75 (3H, OCH_3, s), 2.01 (3H, $COCH_3$, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.49, 159.90, 134.25, 130.10, 124.47, 120.02, 114.43, 114.08, 55.34, 54.04, 23.13.

Compound 5f: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (4H, aromatic protons, m), 6.19 (1H, NH, d), 5.73 (1H, $CHCF_3$, m), 2.04 (3H, $COCH_3$, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.41, 140.66, 133.94, 131.54, 129.60, 128.30, 126.26, 124.36, 122.07, 53.88, 23.12.

Compound 5g: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-6.93 (4H, aromatic protons, m), 6.17 (1H, NH, d), 5.66 (1H, $CHCF_3$, m), 2.03 (3H, $COCH_3$, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.49, 162.83, 135.06, 130.64, 129.03, 124.09, 116.38, 114.98, 53.89, 23.09.

Compound 5h: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.25 (4H, aromatic protons, m), 6.34-5.92 (1H, NH, m), 5.65 (1H, $CHCF_3$, m), 2.01 (3H, $COCH_3$, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.38, 132.85, 129.29, 129.03, 127.89, 123.08, 54.24, 23.19.

Compound 5i: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.25 (5H, aromatic protons, m), 3.49 (1H, $CHCF_3$, m), 3.16 (1H, CH_2Ph, dd), 2.65 (1H, CH_2Ph, dd), 1.55 (2H, NH_2, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.67, 129.27, 128.76, 127.06, 55.15, 36.31.

RESULTS AND DISCUSSION

As shown in **Scheme-I**, α-trifluoromethylated ketones were the crucial intermediates which were formed by the reaction of Weinreb amide with Grignard reagents. Weinreb amide can be easily synthesized from trifluoroacetic anhydride at room temperature with high yield, which avoided very low reaction temperature (-78 °C) starting from ethyl trifluoroacetate and the separation with the unreacted raw material.

With regards to ketones, which could be directly obtained only by distillation in vacuum. In general, oximes exist as solid and can be synthesized by condensation of a ketone with hydroxylamine. In our method, it was used for the nex step without further purification. The oxime were subjected to hydrogenation to produce corresponding α-trifluoromethylated amines with high yield. Under the optimal reaction conditions, the scope of the cascade reaction was then investigated by using a variety of substrates to establish the generality of the process (Table-1).

TABLE-1
SYNTHESIS OF α-TRIFLUOROMETHYLATED AMINES

Entry	R	Yield (%)
a	Me	83
b	Et	80
c		86
d		86
e		82
f		75
g		80
h		81
i		85

The cascade process was found to be broad in scope, with good to excellent yields obtained for all the products (75-86 %). The reaction allowed incorporation of a wide range of functional groups in the α-trifluoromethylated products. The aromatic groups bearing electron-withdrawing or donating groups were both well tolerated, as were substituted aromatic rings. Sterically demanding substrates (Table-1, entry f) and heteroaromatic groups (Table-1, entry g and entry h), were also successfully converted into the corresponding products with excellent yields. More importantly, this cascade protocol is also amenable to scale-up. It was satisfactory that the intermediates ketones and the products amines were easily purified by distillation or crystallization from *n*-hexane/EtOH without requiring chromatographic purification. Therefore, the process for the synthesis of α-trifluoromethylated amines were most suitable to be scaled up and kilogram amounts of the target amines had been prepared successfully.

Conclusion

In summary, we have developed a time and energy economical method for the synthesis of drug-related trifluoromethylated amines. This cascade approach is extremely efficient since the reaction was afforded the desired products with good to excellent yields. Furthermore, this method is operationally simple with wide substrate generality and amenable to scale-up.Notably, the simple and commonly available CF_3 source trifluoro acetic anhydride was employed in trifluoromethylated amines. Therefore, this strategy provides a new general approach for activation and application of trifluoro acetic anhydride. We expect this novel method to be of broad utility in the synthesis of biologically active medicinal agents. We are continuing to explore the mechanism of this reaction with various anhydrides and study the bioactivities of these trifluoromethylated derivatives. The results of these investigations will be reported elsewhere.

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