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Facile preparation of difluoromethyl- and monofluoromethyl-containing amides via Ritter reaction

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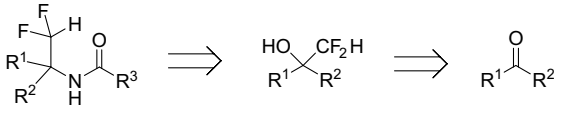
Abstract—Both secondary and tertiary difluoromethylated carbinols were found to readily react with acetonitrile under the catalysis of concentrated sulfuric acid to give the corresponding difluoromethylated acetamides in good yields, which is remarkably more efficient than the previously reported Ritter reactions with corresponding trifluoromethylated carbinols. Similarly, monofluoromethylated and (benzenesulfonyl)difluoromethylated carbinols have shown good reactivity in the Ritter reactions. Since the acetamides can be mildly deacetylated to give amines, the present methodology provides a convenient way for the synthesis of both difluoromethyl- and monofluoromethyl-containing amines starting from simple carbonyl compounds.

During the past two decades, fluorine has been probably the most highlighted halogen element (so-called 'a small atom with a big ego'). Today, around 20% of pharmaceuticals on the market and up to a quarter of those in the development pipeline contain fluorine.[1] The incorporation of fluorine atom(s) into organic molecules can often impart profound and unexpected chemical, biological, and physical properties. Such highly intriguing fluorine effects (also called 'fluorine magic') have spurred organic chemists to develop efficient and convenient methods for the synthesis of fluorine-containing organic molecules.[2] Recently, difluoromethyl (CF_2H) functionality has been realized to be an important group to modulate the biological properties within bioactive molecule, given the fact that the CF_2H group has similar high lipophilicity as trifluoromethyl (CF_3) group, and more importantly, the CF_2H group often behaves as a hydrogen donor through hydrogen bonding and is thus highly useful in applications where a more lipophilic hydrogen bond donor other than hydroxyl (OH) group is required.[2,3] In some cases, the difluoromethylated compounds exhibit increased bioactivity over their trifluoromethylated counterparts.[4] Although several methods for the synthesis of difluoromethylated compounds are available,[5] the reports on the synthesis of difluoromethylated amides **3** are scarce.[5a,6] Previously, we developed the nucleophilic difluoromethylation methods for the efficient synthesis of difluoromethyl alcohols and amines from aldehydes, ketones, and aldimines.[5a,b] Herein, we wish to report our continuing work in the preparation of difluoromethyl amides **3** via Ritter reaction with difluoromethylated carbinols **2** that can be obtained through nucleophilic difluoromethylation of carbonyl compounds **1** (Scheme 1).

Ritter reaction has long been known as a useful approach for the synthesis of amides and amines (after hydrolysis of amides) from alcohols or alkenes.[7] However, although the Ritter reaction has been frequently used in the nonfluorinated systems including the Merck's industrial-scale synthesis of anti-HIV drug Crixivan (indinavir),[8] its application for the preparation of fluorinated amides or amines was not well explored. The Ritter reactions between tertiary trifluoromethylcarbinols **4** (Scheme 2, $R_F = CF_3$; R^1, R^2 = aryl, alkyl, etc.) and acetonitrile under the catalysis of concentrated



3 **2** **1**

Scheme 1.

Keywords: Fluorine; Difluoromethyl; Amide; Ritter reaction.
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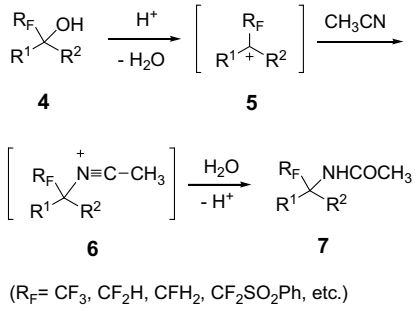
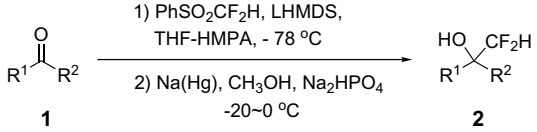


Scheme 2.

sulfuric acid were reported by both Kaluszyner's[6c] and Prakash's groups.[9] However, a similar reaction could not work effectively with secondary trifluoromethylcarbinols (**4**, when $R_F = CF_3$, R^1 or $R^2 = H$).[9,10] Obviously, here the strong electron-withdrawing CF_3 group significantly destabilizes the carbocation species **5**, and R^1, R^2 groups (R^1, R^2 = aryl, alkyl, and other electron-donating groups, but not H) are essentially important to make the reaction proceed (Scheme 2).

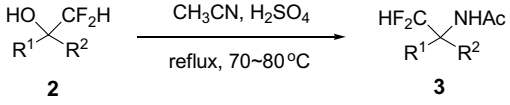
We envisioned that since the difluoromethyl (CF_2H) and monofluoromethyl (CFH_2) groups have relatively weaker electron-withdrawing property, the Ritter reaction with secondary difluoromethylcarbinols and monofluoromethylcarbinols may proceed smoothly. Based on these considerations, we firstly prepared a variety of structurally diverse difluoromethyl-containing carbinols **2a**–**i** in satisfactory to excellent overall yields from corresponding aldehydes and ketones by using the previously reported procedure (Scheme 3).[5c] The Ritter reactions between **2** and acetonitrile were typically performed in the presence of concentrated sulfuric acid as a catalyst at 70–80 °C (Table 1).[11] As we expected, a variety of secondary difluoromethylcarbinols **2a**–**g** could smoothly react with acetonitrile to give the corresponding difluoromethylated acetamides **3a**–**g** (Table 1, entries 1–7). In most cases, the product yields were good to excellent, which is remarkably more efficient than the previously reported similar reactions with trifluoromethylcarbinols.[6c,9] Amidation of difluorocarbinol **2c** occurred via intramolecular rearrangement to give **3c** as the major product (entry 3). The reactions with the tertiary difluorocarbinols **2h** and **2i** gave the amides

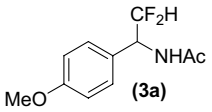
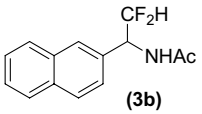
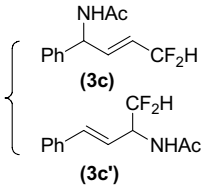
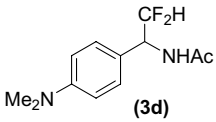
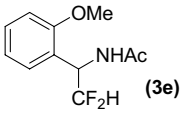
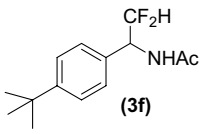
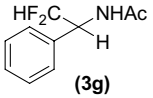
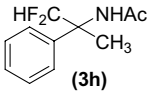
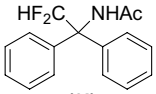


2a: R^1 = H, R^2 = 4-methoxyphenyl (93%)
2b: R^1 = H, R^2 = 2-naphthyl (78%)
2c: R^1 = H, R^2 = (*E*)-PhCH=CH- (69%)
2d: R^1 = H, R^2 = 4-(dimethylamino)phenyl (79%)
2e: R^1 = H, R^2 = 2-methoxyphenyl (86%)
2f: R^1 = H, R^2 = 4-(*tert*-butyl)phenyl (84%)
2g: R^1 = H, R^2 = Ph (66%)
2h: R^1 = CH_3, R^2 = Ph (64%)
2i: R^1 = Ph, R^2 = Ph (62%)

Scheme 3.

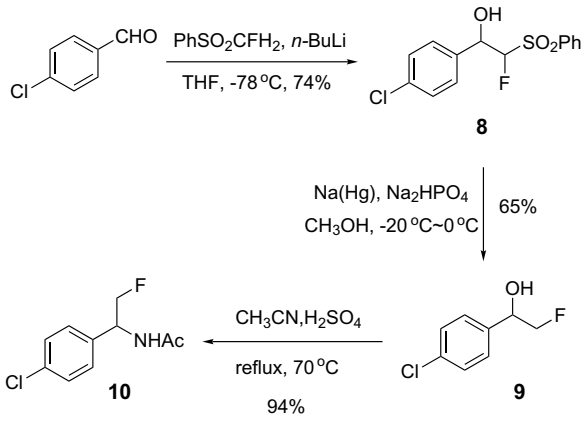
Table 1. Preparation of difluoromethylated amides **1**[11,13]



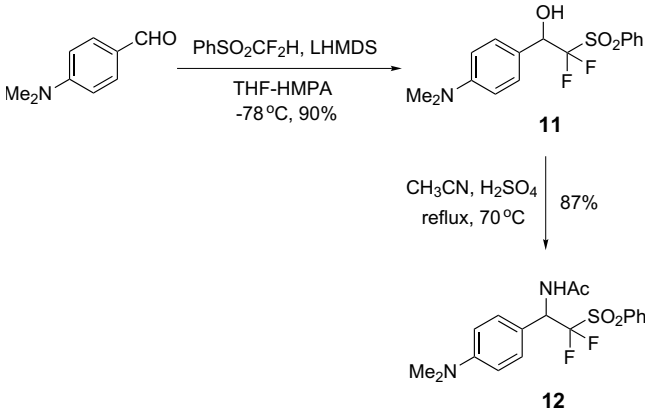
Entry	Carbinol **2**	Product **3**	Yield[a] (%)
1	**2a**	 **(3a)**	97
2	**2b**	 **(3b)**	47
3	**2c**	 **(3c)** **(3c')**	75 Trace
4	**2d**	 **(3d)**	93
5	**2e**	 **(3e)**	92
6	**2f**	 **(3f)**	79
7	**2g**	 **(3g)**	55
8	**2h**	 **(3h)**	82
9	**2i**	 **(3i)**	82

[a] Isolated yield.

3h and **3i** in good yields (entries 8 and 9). Monofluoromethylcarbinol **9** was also prepared and its reaction with acetonitrile under similar Ritter reaction conditions gave the monofluoromethylated amide **10** in 94% yield (Scheme 4). It is noteworthy to mention that in our reactions (as shown in Table 1 and Scheme 4) we did not observe the formation of any dehydrated product



Scheme 4.

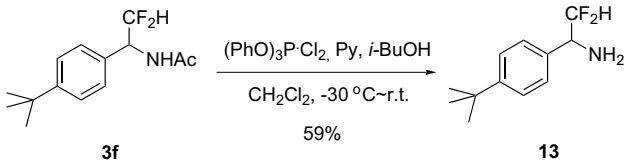


Scheme 5.

1,1-difluoroalkene or 1-fluoroalkene. Kaluszyner et al. found that during the Ritter reactions with dichloromethylcarbinols and methylcarbinols, alkenes were obtained as the major products presumably through an acid-catalyzed dehydration mechanism.[6c]

We also tried the Ritter amidation with (benzenesulfonyl)difluoromethylated carbinol **11**, and the amide product **12** was successfully obtained in 87% yield (Scheme 5).

In order to demonstrate the possibility of further application of these difluoromethylated and monofluoromethylated amides, we converted the difluoromethyl amide **3f** into its free amine form **13**, by using a mild deacetylation procedure reported by Prati and co-workers recently[12] (Scheme 6).



Scheme 6.

In summary, difluoromethylated, monofluoromethylated and (benzenesulfonyl)difluoromethylated amides were successfully prepared with a simple Ritter reaction procedure. Our results indicate that difluoromethyl, monofluoromethyl, and (benzenesulfonyl)difluoromethyl groups are all relatively weaker electron-withdrawing functionalities compared to the trifluoromethyl group, which enabled us to efficiently prepare both secondary and tertiary difluoromethylated (or monofluoromethylated) amides in good yields. Since the difluoromethylated and monofluoromethylated amides can be deacetylated under mild conditions, the present methodology provides a useful approach for the preparation of difluoromethyl- and monofluoromethyl-containing amines.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.07.079.

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10. We also tried the Ritter reaction between 1-(4′-*N*,*N*-dimethylamino)phenyl-2,2,2-trifluoroethanol and acetonitrile under the catalysis of concentrated sulfuric acid. The reaction was messy and we obtained only 35% yield of trifluoromethylated amide product.
11. Typical procedures for the Ritter reaction: into a round-bottom flask, was added difluoromethyl alcohol **2a** (188 mg, 1 mmol) and 10 mL of CH_3CN, then 1 mL of 98% concentrated H_2SO_4 was added. The mixture was refluxed for 3 h. After cooling to room temperature, the reaction mixture was diluted with saturated NaCl solution, and then carefully neutralized with cold saturated aqueous $NaHCO_3$ solution. The solution was extracted with Et_2O three times, and the combined Et_2O phase was dried over $MgSO_4$. After filtration, the solvent was evaporated under vacuum, and the crude product was further purified by silica gel column chromatography to give product **3a** (222 mg, 97% yield) as white solid. Mp 135 °C; ^{1}H NMR: δ 7.28 (d, $J = 8.7$ Hz, 2H), 6.91 (d, $J = 8.7$ Hz, 2H), 6.11–6.14 (m, 1H), 5.99 (t, $J = 55.3$ Hz, 1H), 5.28–5.40 (m, 1H), 3.81 (s, 1H), 2.06 (s, 1H). ^{19}F NMR: δ −126.24 (ddd, $J = 281.8$, 56.7, 16.6 Hz, 1F), −127.28 (ddd, $J = 281.8$, 55.3, 13.8 Hz, 1F). IR (KBr): 3311, 1660, 1615, 1548, 1515, 1440, 1255, 1056 cm^{-1}. Elemental analysis: calcd for $C_{11}H_{13}F_2NO_2$: C, 57.64; H, 5.72; N, 6.11. Found: C, 57.68; H, 5.72; N, 5.96. EI (*m*/*z*, %): 230 (M^++1, 1.01), 209 (50.97), 167 (82.69), 136 (100.00).
12. Spaggiari, A.; Blaszczak, L. C.; Prati, F. *Org. Lett.* **2004**, *6*, 3885–3888.
13. The data for other compounds. Compound **3b**: White solid, mp 160–161 °C. ^{1}H NMR: δ 7.83–7.88 (m, 4H), 7.42–7.52 (m, 3H), 6.11 (t, $J = 54.6$ Hz, 1H), 6.17–6.34 (m, 1H), 5.51–5.65 (m, 1H), 2.10 (s, 1H); ^{19}F NMR: δ −125.08 (ddd, $J = 279.5$, 56.1, 15.3 Hz, 1F), −126.72 (ddd, $J = 279.5$, 55.0, 15.2 Hz, 1F); IR(KBr): 3219, 3058, 1656, 1562, 1510, 1372, 1297, 1060 cm^{-1}. Elemental analysis: calcd for $C_{14}H_{13}F_2NO$: C, 67.46; H, 5.26; N, 5.62. Found: C, 67.57; H, 4.96; N, 5.47; EI (*m*/*z*, %) 229 (M−HF, 73.98), 187 (82.07), 156 (73.98), 43 (100.00). Compound **3c**: White solid, mp 77 °C. ^{1}H NMR: δ 7.25–7.41 (m, 5H), 6.22–6.34 (m, 1H), 6.15 (td, $J = 56.1$, 5.4 Hz, 1H), 5.68–5.94 (m, 3H), 2.04 (s, 1H); ^{19}F NMR: δ −111.65 (m, 1F), −111.85 (m, 1F); IR(KBr): 3317, 1683, 1541, 1498, 1374, 1142, 1014, 971 cm^{-1}. Elemental analysis: calcd for $C_{12}H_{13}F_2NO$: C, 63.99; H, 5.82; N, 6.22. Found: C, 63.91; H, 5.85; N, 6.07; EI (*m*/*z*, %) 225 (0.64), 205 (10.20), 183 (9.36), 132 (76.64), 43 (100.00). Compound **3c**′: White solid, ^{1}H NMR: δ 7.26–7.41 (m, 5H), 6.72 (d, $J = 16.7$ Hz, 1H), 6.09–6.19 (m, 1H), 5.91 (t, $J = 57.5$ Hz, 1H), 5.75–5.87 (m, 1H), 4.97–5.12 (m, 1H), 2.08 (s, 1H); ^{19}F NMR: δ −126.32 (ddd, $J = 283.2$, 55.9, 12.4 Hz, 1F), −129.21 (ddd, $J = 283.2$, 54.7, 18.3 Hz, 1F); IR (KBr): 3315, 1648, 1542, 1374, 1141, 1014, 969 cm^{-1}. Elemental analysis: calcd for $C_{12}H_{13}F_2NO$: C, 63.99; H, 5.82; N, 6.22. Found C, 63.98; H, 5.87; N, 6.01; EI (*m*/*z*, %) 226 (M^++1, 0.75), 204 (30.50), 115 (58.51), 43 (100.00). Compound **3d**: White solid, mp 138 °C. ^{1}H NMR: δ 7.22 (d, $J = 8.6$ Hz, 2H), 6.71 (d, $J = 8.6$ Hz, 2H), 5.99 (t, $J = 55.2$ Hz, 1H), 5.99–6.09 (m, 1H), 5.20–5.38 (m, 1H), 2.96 (s, 6H), 2.05 (s, 3H); ^{19}F NMR: δ −126.11 (ddd, $J = 332.8$, 58.6, 16.9 Hz, 1F), −127.28 (ddd, $J = 332.8$, 55.6, 15.8 Hz, 1F); IR (KBr): 3311, 1656, 1620, 1549, 1528, 1373, 1109, 1060 cm^{-1}. Elemental analysis: calcd for $C_{12}H_{16}F_2N_2O$: C, 59.49; H,6.66; N, 11.56. Found C, 59.33; H, 6.68; N, 11.37; EI (*m*/*z*, %) 242 (11.57), 222 (72.89), 180 (22.24), 149 (100.00). Compound **3e**: White solid, mp 125–127 °C. ^{1}H NMR: δ 7.21–7.41 (m, 2H), 6.89–7.04 (m, 2H), 6.55 (d, $J = 8.6$ Hz, 1H), 6.02 (td, $J = 56.5$, 3.7 Hz, 1H), 5.56–5.72 (m,1H), 3.89 (s, 3H), 2.07 (s, 3H); ^{19}F NMR: δ −122.57 (ddd, $J = 277.8$, 55.8, 10.7 Hz, 1F), −127.38 (ddd, $J = 277.8$, 56.8, 16.1 Hz, 1F); IR (KBr): 3320, 1660, 1549, 1494, 1250, 1122, 1050 cm^{-1}. Elemental analysis: calcd for $C_{11}H_{13}F_2NO_2$: C, 57.64; H, 5.72; N, 6.11. Found: C, 57.64; H, 5.78; N, 6.06; EI (*m*/*z*, %) 229 (0.32), 209 (35.84), 136 (100.00), 121 (21.43). Compound **3f**: White solid, mp 119 °C. ^{1}H NMR: δ 7.42 (d, $J = 8.3$ Hz, 2H), 7.27 (d, $J = 8.3$ Hz, 2H), 6.22–6.10 (m, 1H), 6.01 (td, $J = 55.8$, 2.1 Hz, 1H), 5.31–5.46 (m, 1H), 2.06 (s, 3H), 1.31 (s, 9H); ^{19}F NMR: δ −125.46 (ddd, $J = 281.2$, 56.3, 16.1 Hz, 1F), −127.01 (ddd, $J = 281.2$, 55.1, 15.5 Hz, 1F); IR (KBr): 3265, 2964, 1659, 1556, 1394, 1082 cm^{-1}. Elemental analysis: calcd for $C_{14}H_{19}F_2NO$: C, 65.86; H, 7.50; N, 5.49. Found: C, 65.92; H, 7.63; N, 5.47; EI (*m*/*z*, %) 235 (M^+−HF, 69.78), 193 (100.00), 162 (85.99), 91 (27.93). Compound **3g**: White solid, ^{1}H NMR: δ 7.38 (m, 5H), 6.29 (m, 1H), 6.03 (t, $J = 55.5$ Hz, 1H), 5.35–5.48 (m, 1H), 2.08 (s, 3H); ^{19}F NMR: δ −125.65 (ddd, $J = 282.7$, 56.5, 16.4 Hz, 1F), −127.35 (ddd, $J = 282.7$, 55.1, 14.4 Hz, 1F); IR (KBr): 3325, 1660, 1547, 1499, 1372, 1115 cm^{-1}. Elemental analysis: calcd for $C_{10}H_{11}F_2NO$: C, 60.30; H, 5.57; N, 7.03. Found: C, 60.25; H, 5.61; N, 6.97; EI (*m*/*z*, %) 200 (M^++1, 0.92), 179 (25.25), 106 (100.00). Compound **3h**: White solid, mp 116 °C. ^{1}H NMR: δ 7.22–7.52 (m, 5H), 6.38 (t, $J = 56.4$ Hz, 1H), 6.02 (s, 1H), 2.02 (s, 3H), 1.77 (s, 3H); ^{19}F NMR: δ −128.35 (dd, $J = 277.2$, 55.9 Hz, 1F), −129.79 (dd, $J = 277.2$, 55.9 Hz, 1F); IR(KBr): 3281, 3080, 1654, 1553, 1498, 1372, 1208, 1108 cm^{-1}. Elemental analysis: calcd for $C_{11}H_{13}F_2NO$: C, 61.96; H, 6.15; N, 6.57. Found: C, 61.96; H, 6.33; N, 6.54; EI (*m*/*z*, %) 213 (4.62), 162 (44.74), 120 (100.00). Compound **3i**: White solid. ^{1}H NMR: δ 7.31–7.39 (m, 10H), 7.14 (t, $J = 56.7$ Hz, 1H), 6.46 (s, 1H), 2.01 (s, 3H); ^{19}F NMR: δ −123.32 (d, $J = 56.2$ Hz, 2F); IR (KBr): 3256, 3060, 1654, 1546, 1498, 1069 cm^{-1}. Elemental analysis: calcd for $C_{16}H_{15}F_2NO$: C, 69.81; H, 5.49; N, 5.09. Found: C, 69.74; H,5.53; N, 4.91; EI (*m*/*z*, %) 275 (1.32), 182 (100.00), 104 (30.06).