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TRIFLUOROACETIMIDOYL CHLORIDES AS A NEW TRIFLUOROMETHYL BUILDING BLOCK FOR FLUORINATED NITROGEN HETEROCYCLES

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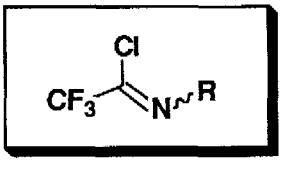
Summary: N-Substituted trifluoroacetimidoyl chlorides have been prepared and allowed to react with various carbon nucleophiles, affording trifluoromethyl ketimines.

Organofluorine compounds have accepted an increasing attentions.[1] Among them, preparations of trifluoromethylated compounds are in great demand because of their unique nature for biological activities and high performance material science. Trifluoroacetic acid is one of the most available and economically feasible starting materials for trifluoromethylated compounds. However, carbon-carbon bond formation by nucleophilic substitution on the carbonyl group is not straightforward except for Friedel-Crafts type trifluoroacetylation[2], and nucleophilic substitution of trifluoroacetic acid,[3] the esters[4], and the amides[5]. Here, we describe preparation and reactions of N-substituted trifluoroacetimidoyl chlorides 1 useful for the fluorinated nitrogen heterocycles, in which chlorine acts as an element replaceable with carbon nucleophiles.



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N-Alkyl, N-aryl, and N-carbomethoxyimidoyl chlorides 1 can be prepared by the action of phosphorus pentachloride with N-substituted trifluoroacetamides.[6], [7] Imidoyl chlorides in general are so sensitive to moisture to be easily hydrolyzed upon exposure to an open atmosphere.[8] In contrast, trifluoroacetimidoyl chlorides are so stable imines to be handled without any difficulty presumably because of the strong electron-withdrawing nature of trifluoromethyl group.[9] In fact, **1b** (R=p-methylphenyl) was totally recovered

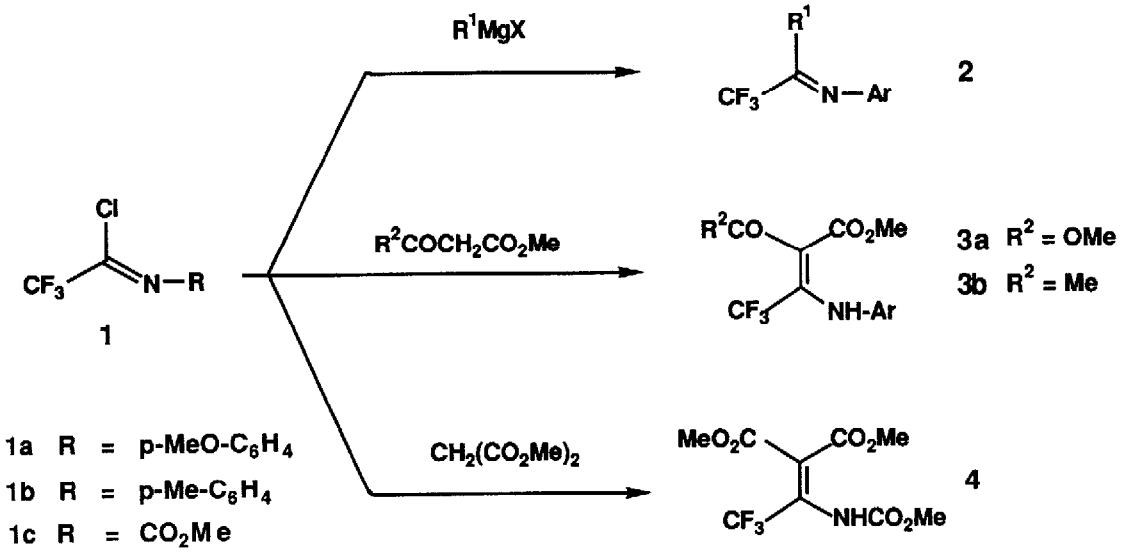
after passing a short silica gel column. On hydrolyzing **1b** (R=p-methylphenyl) in acetone-water (5:1) at room temperature, the ^{19}F-NMR reveals no change in one hour and 10 % conversion to the corresponding amide after three days, meanwhile N-cyclohexylacetimidoyl chloride decomposes instantaneously.[8] the ^{19}F-NMR of **1a**(R=p-methoxyphenyl) shows a singlet suggesting a single isomer of which geometry is not clear at this moment.

N-(p-Methoxyphenyl)trifluoroacetimidoyl chloride **1a** reacts with Grignard reagents in THF or ether at room temperature to give the corresponding imines of 1,1,1-trifluoro-2-alkanones **2** in good yields as shown in Table 1. It is noteworthy that the alkylation to the chloride **1a** is much faster than that to the product imines **2**. Other carbon nucleophiles such as active methylene compounds undergo smooth replacement of chlorine, affording carboxylates **3** (**3a** R^2=MeO, **3b** R^2=Me) which are precursors of amino acids and nitrogen heterocyclic compounds bearing trifluoromethyl group. N-Methoxycarbonyltrifluoroacetimidoyl chloride **1c** reacts also with dimethyl malonate in THF to give the enamine **4** in 82 % yield. Products obtained from active methylene compounds are enamines rather than imines presumably because of the thermodynamic stability of the β-amino-α,β-unsaturated ester moiety.

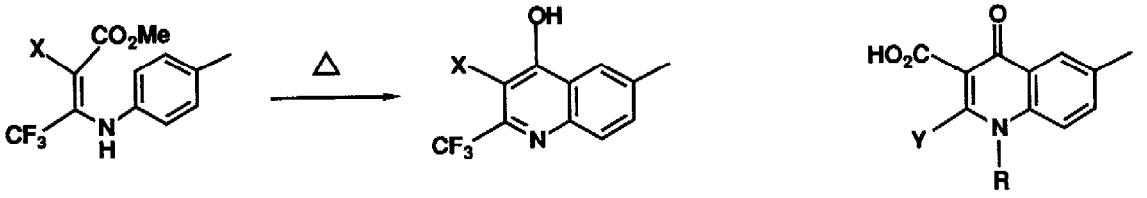
Table 1 Reaction of 1 with Carbon Nucleophiles[a]

Entry	1	Nucleophile	Solvent	Product	(Yield %)
1	**1a**	CH_3CH_2MgBr	Ether	**2**	(83)
2	**1a**	CH_2=CHMgBr	THF	**2**	(76)
3	**1a**	CH_2=$CHCH_2MgBr$	Ether	**2**	(85)
4	**1a**	n-$C_8H_{17}MgBr$	THF	**2**	(80)
5	**1a**	$PhCH_2MgCl$	Ether	**2**	(61)
6	**1b**	$CH_2(CO_2CH_3)_2$/NaH	THF	**3a**	(67)
7	**1b**	$CH_3COCH_2CO_2CH_3$/NaH	THF	**3b**	(65)
8	**1c**	$CH_2(CO_2CH_3)_2$/NaH	THF	**4**	(82)

a) Substrate 1 (0.42 mmol) in 2 ml of solvent at room temperature for 30 min.



Thermal cyclization of enamines **3a** (R^2=MeO) in cumene at 200 °C and **3b** (R^2=Me) at 250 °C provides 3-substituted-4-hydroxy-2-trifluoromethylquinoline derivatives **5a** and **5b** in 66 % and 70 % yields, respectively.[10),11),12)] Hydrolysis of methoxycarbonyl group of **5a** leads to the formation of **5c**, 2-trifluoromethyl derivative of quinolone carboxylic acids **6a**, a potent antibiotics.[13)]



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5a X = CO_2Me

5b X = COMe

5c X = CO_2H

6a Y = H

6b Y = CF_3

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12) **5a**: IR(nujol) 3050 (OH), 1738 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 Hz) δ=2.56 (s, 3H, CH_3), 4.06(s, 3H, OCH_3), 7.71(dd, J_1=8.6 Hz, J_2=2.0 Hz, 1H, ArH), 8.00(d, J=8.6 Hz, 1H, ArH), 8.13(broad s, 1H, ArH), 12.7(m, 1H, OH); **5b**: IR(nujol) 3080 (OH), 1702(C=O) cm^{-1}; ^{1}H-NMR(DMSO-d_6, 500 Hz) δ=2.47(s, 3H, CH_3), 2.52(s, 3H, CH_3), 7.59(dd, J_1=8.6 Hz, J_2=1.8 Hz, 1H, ArH), 7.79 (d, J=8.6 Hz, 1H, ArH), 7.96(s, 1H, ArH), 12.5(broad s, 1H, OH).

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