Regioselective Synthesis of 5-Trifluoromethyl Pyrazoles by the [1+4] Cyclization of Phenylhydrazones with N-Aryl Trifluoroacetimidoyl Iodides

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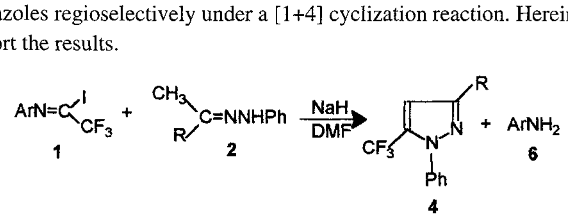
Abstract: Treatment of the phenylhydrazone of a methyl ketone (**2**) or cyclohexanone (**3**) with N-aryl trifluoroacetimidoyl iodide (**1**) in the presence of excess sodium hydride resulted in a [1+4] cyclization to give 5-trifluoromethyl pyrazoles (**4**, **5**) regioselectively. The structure of products **4** or **5** was confirmed by the ^{13}C NMR spectra.

Trifluoromethyl pyrazoles are of considerable interest in agrochemical and medicinal fields due to their herbicidal,[1] fungicidal,[2] insecticidal,[3] analgetic, antipyretic, and antiinflammatory properties.[4] Although many kinds of trifluoromethyl pyrazoles have been synthesized and utilized, the synthetic methods mainly involved [3+2] cyclizations such as the classical hydrazine-β-diketone[5] or hydrazine-trifluoromethylacetylenes[6] route and 1,3-dipolar cycloaddition to alkene.[7] Most of these reactions gave two regioisomers (3 and 5-trifluoromethyl pyrazoles) or/and hydroxy pyrazoline.[8] Therefore regioselective synthesis of 3 or 5-trifluoromethyl pyrazoles without byproduct would be of much interest. Recently selective protected trifluoromethyl β-diketones were reported to give 5-trifluoromethyl pyrazoles regioselectively.[9] However, the report on [1+4] cyclic reaction to regioselective trifluoromethyl pyrazoles is limited. In our continuing investigation on the chemical conversion of N-aryl per(poly)fluoroalkyl imidoyl iodides[10] as a fluorine-containing building block,[11] we found that N-aryl trifluoroacetimidoyl iodide (**1**) can be converted to 5-trifluoromethyl pyrazoles regioselectively under a [1+4] cyclization reaction. Herein we report the results.



Scheme 1

N-Phenyl hydrazone of a methyl ketone was treated with 2.2 molar equivalents of sodium hydride in anhydrous DMF at room temperature under nitrogen. The resulting dianion was then allowed to react with 1 molar equivalent of N-aryl trifluoroacetimidoyl iodide (**1**) to give the product **4** and an aryl amine (**6**).[12] (**Scheme 1, Table 1**).

The structure of compounds **4** was established by the ^{1}H NMR, ^{19}F NMR, ^{13}C NMR, MS, HRMS and IR spectra. They were N-phenyl trifluoromethyl pyrazole derivatives. Analysis of the ^{13}C NMR spectra of compound **4** provided valuable information on the position of the trifluoromethyl group on pyrazole ring (**Table 2**). The CF_3 carbon appeared at about 120ppm (q, $^{1}J_{C-F}$=268-270Hz) indicated that the CF_3 group was located at either 3 or 5 position of the pyrazole. In addition, the ring carbon bearing the CF_3 group at about 132-134ppm (q, $^{2}J_{C-F}$=39Hz) confirmed the locating of CF_3 group at position 5 in all cases.[13]

In this reaction, N-aryl trifluoroacetimidoyl iodide (**1**) served as an electrophile to accept the 1, 4-dianion of the methyl ketone hydrazone. The strong electron-withdrawing power of CF_3 group facilitated the cleavage of iodide ion and an aryl amine from compound **1** during the nucleophilic attack of the dianion. This reaction constituted a formal [1+4] cyclic reaction between compound **1** (1 atom fragment) with 1, 4-dianion of the methyl ketone (4 atom fragment). Thus, N-aryl trifluoroacetimidoyl iodide could be regarded as a CF_3C building block in this reaction which was different from that reported previously.[14] The reaction proceeded more quickly for N-phenyl trifluoroacetimidoyl iodide (**1b**) than N-(*p*-methoxyphenyl) trifluoroacetimidoyl iodide (**1a**) or N-(*p*-chlorophenyl) trifluoroacetimidoyl iodide (**1c**). In addition, the yield was relatively low for Entry 7 due to the presence of the bulky *tert*-butyl group in **2c** (**Table 1**).

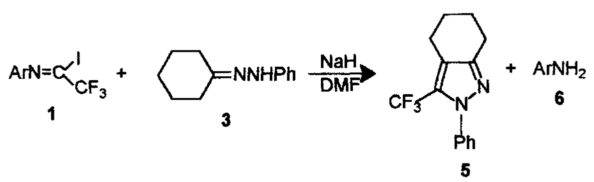
Table 1. 5-Trifluoromethyl Pyrazoles from N-Aryl Trifluoroacetimidoyl Iodides and Phenylhydrazones

Entry	Imidoyl Iodide, 1 Ar=	Hydrazone, 2 R=	T ((C)	Time	4/(%)^a
1	*p*-$CH_3OC_6H_4$, **1a**	Ph, **2a**	r.t.	20 min	**4a**/72
2	Ph, **1b**	Ph, **2a**	r.t.	10 min	**4a**/70
3	*p*-ClC_6H_4, **1c**	Ph, **2a**	r.t.	20 min	**4a**/57
4	*p*-$CH_3OC_6H_4$, **1a**	2-Furyl, **2b**	r.t.	20 min	**4b**/67
5	Ph, **1b**	2-Furyl, **2b**	r.t.	10 min	**4b**/81
6	*p*-ClC_6H_4, **1c**	2-Furyl, **2b**	r.t.	20 min	**4b**/75
7	*p*-$CH_3OC_6H_4$, **1a**	t-Bu, **2c**	r.t.	2 h	**4c**/28
8	*p*-$CH_3OC_6H_4$, **1a**	**3**	40	10 h	**5**/71
9	Ph, **1b**	**3**	40	4 h	**5**/62
10	*p*-ClC_6H_4, **1c**	**3**	40	4 h	**5**/50

a: isolated yields

Table 2. The ^{13}C NMR of C^5 and CF_3 of Compounds **4** and **5**

Entry	Product	^{13}C NMR (ppm) of C^5	^{13}C NMR (ppm) of CF_3
1	**4a**	134.0 (q, J=39Hz)	119.9 (q, J=269Hz)
2	**4b**	133.7 (q, J=39Hz)	119.7 (q, J=270Hz)
3	**4c**	132.1 (q, J=39Hz)	120.6 (q, J=268Hz)
4	**5**	133.7 (m)	119.7 (q, J=269Hz)



Scheme 2

The reaction between the phenyl hydrazone of cyclohexanone (**3**) and N-aryl trifluoroacetimidoyl iodide (**1**) in the presence of sodium hydride required a longer reaction time at a higher temperature (**Scheme 2, Table 1**). The pyrazole derivative **5** was obtained whose ^{13}C NMR was similar to that of compound **4**. Unexpectedly, all attempts at the conversion of N-aryl derivatives of higher homologues of poly(per)fluoroalkyl imidoyl iodide to the corresponding pyrazoles failed.

In conclusion, we achieved a regioselective synthesis of 5-trifluoromethyl pyrazoles with the [1+4] cyclization reaction of N-aryl trifluoroacetimidoyl iodides with phenyl hydrazones of methyl ketones or cyclohexanone. It not only provided a new synthetic method for the fluoro-pyrazoles but also broadened the synthetic application of trifluoroacetimidoyl iodide. Trifluoroacetimidoyl iodide served as a CF_3C building block for the formation of trifluoromethyl heterocycles.

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12. Selective data for **4**. **4b**:oil, δH(300MHz, $CDCl_3$) 7.56-7.47 (m, 6H, Ar-H), 7.05 (s, 1H, C^4-H), 6.81 (1H, d, J=3.6Hz, Ar-H), 6.50-6.48 (m, 1H, Ar-H), ppm; δF (56.4MHz, $CDCl_3$, TFA as external standard) -20.0 (CF_3) ppm; δC (75.5MHz, $CDCl_3$) 147.2, 144.3, 142.6, 139.0, 133.7 (q, $^2J_{C-F}$=39Hz, C^5), 129.5, 129.1, 125.9, 119.7 (q, $^1J_{C-F}$=270Hz, CF_3), 111.5, 107.2, 105.9 (q, $^3J_{C-F}$=2.3Hz, C^4), IR (v, cm^{-1}) 3130, 3065, 1587, 1500, 1300, 1290, 1230, 1172, 1140; MS: 278 (M^+, 100.00), 77 (Ph, 18.30); HRMS for $C_{14}H_9F_3N_2O$: 278.0662.
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