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A new and simple approach to N-substituted trifluoroacetimidoyl aryl ketones

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Abstract

Using 1,3-dimethylimidazolium iodide as a catalyst, the reaction of trifluoroacetimidoyl chloride with an aromatic aldehyde in the presence of sodium hydride gives *N*-substituted trifluoroacetimidoyl aryl ketones.

Keywords: Trifluoroacetimidoyl aryl ketones; Trifluoroacetimidoyl chloride; Aroylation; NMR spectroscopy; IR spectroscopy; Mass spectrometry

1. Introduction

Trifluoromethylated compounds are of great importance in medicine, agricultural and materials science [1]. The development of methods for introducing trifluoromethyl groups into a molecule receives increasing attention, the building block strategy is, moreover, of particular interest [2]. Trifluoromethyl ketones are expected to be good synthetic blocks for such a purpose because of the versatile transformations of the carbonyl group. The preparations of trifluoromethyl ketones have been recently reviewed [3]; however, the synthesis of acyl trifluoromethyl ketones or their synthetic equivalents has not been easy.

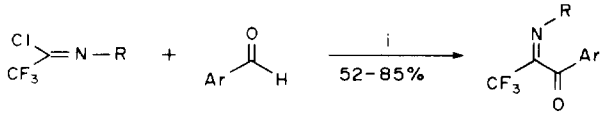
Very recently, Uneyama and co-workers reported the generation of *N*-aryltrifluoroacetimidoyl lithium by an iodine–lithium exchange reaction between *N*-aryltrifluoroacetimidoyl iodide and ^{n}BuLi [4]. They trapped this unstable species with acyl chloride, providing *N*-aryltrifluoroacetimidoyl aryl/alkyl ketones. This methodology, however, shows some limitations since low temperature (-100 °C to -78 °C) is essential for stabilizing labile trifluoroacetimidoyl lithium and only *N*-aryl imino ketones can be obtained. Moreover, the substituent on the *N*-phenyl ring markedly affects the reaction process.

Herein we wish to report our studies on the aroylation of trifluoroacetimidoyl chloride with aromatic aldehydes, providing *N*-substituted trifluoroacetimidoyl aryl ketones. It is noteworthy to emphasize that in our procedure, trifluoroacetimidoyl chloride behaves as a carbocation equivalent compared with the carbanionic nature of the trifluoroacetimidoyl species as employed in Uneyama's method. The resulting trifluoroacetimidoyl aryl ketones are trifluoromethylated 1,2-dicarbonyl synthetic equivalents, which can be used in the synthesis of a wide variety of organic compounds bearing the trifluoromethyl moiety.

2. Results and discussion

Reactions of trifluoroacetimidoyl chloride with carbon nucleophiles have been investigated [5]. We tried to extend the field of application of this reaction to aroyl anions (Arc=O) and found that the latter attacked the C=N bond of the imidoyl chloride molecules and then displaced the chlorine to afford trifluoroacetimidoyl ketones.

As shown in Scheme 1 and Table 1, a series of benzaldehydes with various nuclear substituents in different positions reacted smoothly with trifluoroacetimidoyl chloride under the conditions given in the title to the scheme, providing trifluoroacetimidoyl aryl ketones in satisfactory yield (see Table 2). The formation of compounds **3a** and **3b** demonstrated that *N*-substituents in trifluoroacetimidoyl chloride molecule



1 2 3

Scheme 1. (i) 1,3-Dimethylimidazolium iodide (10% equiv.), NaH, THF, 0 °C, 1.5–5 h.

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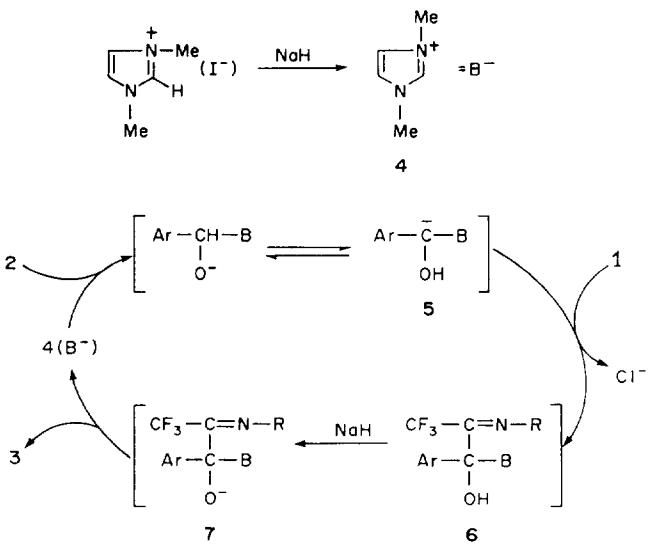
Table 1
Trifluoroacetimidoyl aryl ketones prepared

Compound	R	Ar	Compound	R	Ar
3a	C_6H_5	C_6H_5	**3f**	n-C_8H_{17}	*p*-ClC_6H_4
3b	n-C_8H_{17}	C_6H_5	**3g**	n-C_8H_{17}	*m*-ClC_6H_4
3c	n-C_8H_{17}	*p*-MeC_6H_4	**3h**	n-C_8H_{17}	*o*-ClC_6H_4
3d	n-C_8H_{17}	*p*-$MeOC_6H_4$	**3i**	n-C_8H_{17}	*p*-$NO_2C_6H_4$
3e	n-C_8H_{17}	*p*-FC_6H_4			

Table 2
Preparation conditions and spectral characteristics of compounds **3**

Compound	Reaction time (h)	Yield (%)	Molecular formula	IR (film) ν(C=O) (cm^{-1})	^{19}F NMR δ (ppm)	MS (M+1)
3a	5	69	$C_{15}H_{10}F_3NO$ (277.2)	1680	−8.24	278
3b	5	52	$C_{17}H_{22}F_3NO$ (313.4)	1674	−9.30	314
3c	4	60	$C_{18}H_{24}F_3NO$ (327.4)	1686; 1598	−9.24	328
3d	4	52	$C_{18}H_{24}F_3NO_2$ (343.4)	1678; 1590	−9.30	344
3e	3.5	58	$C_{17}H_{21}F_4NO$ (331.4)	1680	−9.20; 36.9	332
3f	4.5	73	$C_{17}H_{21}ClF_3NO$ (347.8)	1678	−9.24	348 (M)
3g	4	64	$C_{17}H_{21}ClF_3NO$ (347.8)	1670	−9.12	348 (M)
3h	5	74	$C_{17}H_{21}ClF_3NO$ (347.8)	1672	−9.20	348 (M)
3i	1.5	85	$C_{17}H_{21}F_3N_2O_3$ (358.4)	1680; 1520, 1350 (NO_2)	−9.34	359



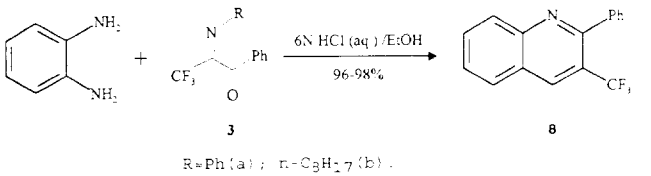
Scheme 2.

did not cause any pronounced difference in this reaction. We selected *N*-(n-octyl)trifluoroacetimidoyl chloride as the starting material instead of the *N*-phenyl derivatives described by Uneyama et al. [4] for ease of identification of the products by ^1H NMR spectroscopy. In this chemical transformation, 1,3-dimethylimidazolium iodide was found to be a catalyst since without its participation the reaction failed to give a aroylation product. Aliphatic aldehydes could not be used in this reaction due to the aldol condensation.

The formation of aroyl derivatives **3** seemed to proceed through the ylide **4** as the result of the interaction of NaH on the C-2 hydrogen of 1,3-dimethylimidazolium iodide. The ylide thus formed attacked the aldehyde to give an *O*-anion species which is in equilibrium with the corresponding carbanion **5**. The latter displaced the chlorine of imidoyl chloride to derive the intermediate **6**, which upon treatment with NaH generated a new *O*-anion intermediate **7**. By expulsion of the ylide **4** from *O*-anion **7**, the aroyl product was formed.

Scheme 2 illustrates this transformation. In this case, the generation of the key intermediate carbanion **5** is similar to the classic benzoin condensation reaction.

The resulting trifluoroacetimidoyl aryl ketones **3a** and **3b** were transformed to the 2-trifluoromethyl-3-phenylquinoxaline **8** by treatment with 1,2-phenylenediamine in ethanol in the usual manner [6].



3 8

R=Ph (a); n-C_8H_{17} (b).

3. Experimental details

The melting point of compound **8** is uncorrected. IR spectra were recorded on a Shimadzu-440 spectrophotometer. ^1H and ^{19}F NMR spectra were taken on a Varian EM 360A spectrometer. Chemical shifts for ^1H NMR spectra are reported in ppm downfield from TMS. ^{19}F NMR spectra were obtained using CF_3CO_2H as an external standard, positive for upfield shifts. EI-MS were recorded on an HP5989A mass spectrometer.

N-substituted trifluoroacetimidoyl chlorides [7] were prepared by refluxing a mixture of trifluoroacetic acid and a primary amine in CCl_4 in the presence of Et_3N and Ph_3P. 1,3-Dimethylimidazolium iodide [8] was prepared from MeI and 1-methylimidazole (from Tokyo Kasei). NaH was purchased from Merck Co. Other reagents were commercially available from a local source (Shanghai Chemical Co.). THF was freshly distilled from sodium benzophenone ketyl.

3.1. N-(n-Octyl)trifluoroacetimidoyl phenyl ketone (3b): typical procedure

To an oven-dried two-necked 50 ml round-bottom flask fitted with a magnetic stirring bar and charged with dry N_2 was added NaH (165 mg, 5.5 mol, 80% in mineral oil) and THF (20 ml). To the resulting stirred suspension was added successively benzaldehyde (0.55 ml, 5.5 mol), *N*-(n-octyl)-2,2,2-trifluoroacetimidoyl chloride (1.22 g, 5 mmol) and 1,3-dimethylimidazolium iodide (112 mg, 0.5 mmol) at 0 °C. The resulting mixture was then stirred at room temperature for 5 h. Completion of reaction was monitored by TLC. After quenching with aq. NH_4Cl (10 ml), the resulting mixture was partitioned between Et_2O (20 ml) and sat. aq. NaCl (20 ml). The organic layer was separated and the aqueous layer extracted with Et_2O (3×20 ml). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to give the crude product, which was subjected to column chromatography on silica gel (eluent: 30% benzene in petroleum ether) to give 0.81 g of pure **3b** as an oil.

Table 3
^1H NMR spectra of compounds **3**

Compound	^1H NMR (CCl_4) δ (ppm), J (Hz)
3a	7.49–7.08 (10H)
3b	7.90–7.40 (m, 5H, C_6H_5); 3.50–3.20 (m, 2H, NCH_2); 1.69–1.49 (m, 2H); 1.43–1.23 (m, 10H); 0.86 (t, 3H, J=6.7)
3c	7.67–7.48 (m, 2H); 7.50–7.30 (m, 2H); 3.54–3.20 (m, 2H, NCH_2); 2.32 (s, 3H, Me); 1.72–1.54 (m, 2H); 1.40–1.18 (m, 10H); 0.86 (t, 3H, J=6.7)
3d	7.93–7.63 (m, 2H); 7.13–6.83 (m, 2H); 3.93 (s, 3H, MeO); 3.52–3.18 (m, 2H, NCH_2); 1.68–1.50 (m, 2H); 1.40–1.20 (m, 10H); 0.85 (t, 3H, J=6.7)
3e	7.86–7.78 (m, 2H); 7.51–7.43 (m, 2H); 3.54–3.18 (m, 2H, NCH_2); 1.70–1.50 (m, 2H); 1.46–1.24 (m, 10H); 0.86 (t, 3H, J=6.6)
3f	7.83–7.73 (m, 2H); 7.55–7.47 (m, 2H); 3.52–3.20 (m, 2H, NCH_2); 1.69–1.49 (m, 2H); 1.46–1.26 (m, 10H); 0.88 (t, 3H, J=6.2)
3g	7.78–7.36 (m, 4H); 3.54–3.22 (m, 2H, NCH_2); 1.68–1.46 (m, 2H); 1.43–1.20 (m, 10H); 0.90 (t, 3H, J=6.8)
3h	7.84–7.60 (m, 4H); 3.56–3.26 (m, 2H, NCH_2); 1.64–1.40 (m, 2H); 1.44–1.26 (m, 10H); 0.86 (t, 3H, J=6.8)
3i	8.43–8.27 (m, 2H); 8.10–7.93 (m, 2H); 3.80–3.40 (m, 2H, NCH_2); 1.78–1.56 (m, 2H); 1.54–1.32 (m, 10H); 0.96 (t, 3H, J=6.6)

Table 4
Microanalysis data for compound **3**

Compound	Calculated (%)			Found (%)		
	C	H	N	C	H	N
3a	64.99	3.63	5.05	64.72	3.76	5.15
3b	65.14	7.08	4.47	65.02	7.12	4.55
3c	66.03	7.39	4.28	66.32	7.36	4.25
3d	62.95	7.04	4.08	62.74	7.24	4.18
3e	61.61	6.39	4.23	61.67	6.52	4.03
3f	58.70	6.09	4.03	58.54	6.19	4.18
3g	58.70	6.09	4.03	58.62	6.12	4.16
3h	58.70	6.09	4.03	58.68	6.14	4.02
3i	56.97	5.91	7.82	57.00	5.84	8.16

3.2. 2-Trifluoromethyl-3-phenylquinoxaline (8)

To a mixture of **3b** (1.22 g, 3.97 mmol) and 1,2-phenylenediamine (0.42 g, 3.97 mmol) in EtOH (15 mol) was added 6 N HCl (aq.) (8 ml), and the mixture then stirred for 36 h at room temperature. The reaction mixture was extracted with ether (3×30 ml). The organic layers were dried (Na_2SO_4), filtered and concentrated to give the crude product

which upon column chromatography on silica gel (eluent: 30% benzene in petroleum ether) gave 1.03 g of **8** in 96% yield, m.p. 114 °C. ^{19}F NMR (CCl_4, TFA) δ: −16.7 ppm. Analysis: Calc. for $C_{15}H_9F_3N_2$: C, 65.69; H, 3.31; H, 10.22%. Found: C, 65.47; H, 3.40; N, 10.14%.

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