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A new synthesis of substituted 2-trifluoromethylindoles

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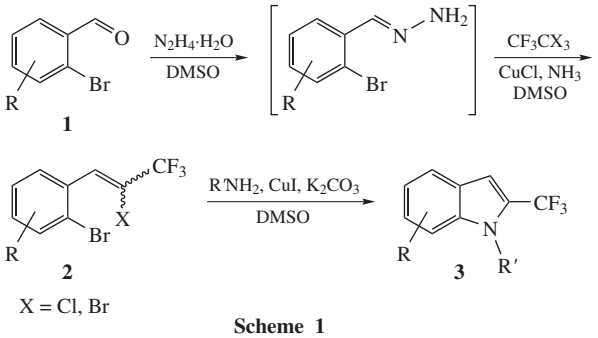
The one-pot synthesis of substituted 2-trifluoromethylindoles from β-halo-β-(trifluoromethyl)-(*o*-halostyrene) and primary amines is based on a Cu^{I}-catalysed double nucleophilic substitution reaction.

The replacement of a methyl group or chlorine atom with a trifluoromethyl group in the molecules of pharmaceutical substances is widely used for a new drug development. Such change of substance structure allows one, as a rule, to keep its primary biological activity and to improve pharmacokinetical properties due to the unique stability of trifluoromethyl group *in vivo*.[1] Therefore, an elaboration of new selective methods of synthesis of CF_3-substituted products is an actual problem.[2] There are some recent examples of new perspective pharmacological substances containing 2-trifluoromethylindole fragments: chemokine receptor 5 antagonist,[3] general anesthesia inducer,[4] tyrosine kinase inhibitor[5] and some perspective antineoplastic agents.[6]

Various methods of 2-trifluoromethylindoles synthesis were elaborated last decades, they include the interaction of aromatic nitrones with trifluoromethyl substituted alkynes; modified Madelung reaction application;[8] trifluoromethyl radicals addition to indole system;[9] intramolecular reactions of trifluoroacetylimidoyl radical with triple bond;[10,11] reductive coupling of some oxamides using titanium salts;[12,13] catalytic thermolysis of some 2-*N*-trifluoroacetylaminobenzylmethyl esters;[14] intramolecular palladium-catalysed coupling of 2-iodophenyltrifluoroacetylamides;[15,16] Wittig and Heck reactions of some 2-halotrifluoroacetylanilides;[17,18] synthesis using 2-halotrifluoroacetylanilides and ketoesters[19] and some examples of 2-trifluoromethylindole containing molecules modification.[20,21]

Earlier, a new catalytic olefination reaction was discovered by our research group.[22] N-Unsubstituted hydrazones of aldehydes or ketones can be transformed into various halogen-substituted alkenes upon treatment with polyhaloalkanes in the presence of a base and catalytic amounts of copper salts. Advantages of this method are inexpensive starting compounds and simplicity of products isolation. The β-halo-β-(trifluoromethyl)styrenes can be easily obtained from corresponding benzaldehydes and perhaloalkanes *via* catalytic olefination reaction.[23] This reaction does not require an inert atmosphere and an excess of organometallic or organophosphorus compounds as, for example, the Wittig-type reactions,[24,25] or the aldol-type reaction of benzaldehyde with fluoromethyl phenyl sulfone in the presence of *n*-butyl lithium and subsequent dehydration. [26]

We proposed that β-halo-β-(trifluoromethyl)styrenes with a halogen atom in the *ortho*-position can be used as precursors for 2-trifluoromethylindoles synthesis. Simultaneous nucleophilic substitution of vinyl and aryl halogen atoms by primary amines can open simple way to 2-trifluoromethylindoles bearing substituents at the 1-position and in the aromatic ring. This work



Scheme 1

is devoted to the development of a new reaction scheme of 2-trifluoromethylindoles synthesis based on double nucleophilic replacement of halogen atoms in trifluoromethyl-substituted β-halo-(*o*-halostyrenes). A similar cyclization for nonfluorinated indole synthesis was catalyzed by $Pd_2(dba)_3$ and a phosphine ligand system.[27]

We have prepared a number of alkenes, β-halo-β-(trifluoromethyl)styrenes, from *ortho*-bromo substituted benzaldehydes[23] and studied a model reaction with *n*-hexylamine using $Pd(PPh_3)_4$ or Pd·MeCN as a catalyst. If Bu^tOK was used as the base, the nucleophilic replacement of vinyl bromine by *tert*-butoxy group took place.

We found that the reaction proceeds smoothly with various amines in the presence of K_2CO_3 and copper iodide as a catalyst (Scheme 1, Table 1).[†] As a result, corresponding 2-trifluoroindoles **3** can be prepared in reasonable yields in two steps starting from *ortho*-bromobenzaldehydes **1**. Variation of amine component permits variation of substituents at indole nitrogen.

Table 1 Synthesis of 2-trifluoromethylindoles **3a–l**.

Compound	R	R′	Yield of **3** (%)
3a	H	*n*-C_6H_{13}	60
3b	5-MeO	*n*-C_6H_{13}	40
3c	H	2-phenylethyl	58
3d	H	2-methoxyethyl	49
3e	H	3-methoxypropyl	48
3f	H	2-(3,4-diethoxyphenyl)ethyl	53
3g	H	Pr^i	39
3h	H	Et	50
3i	5-MeO	Et	65
3j	5-EtO	Et	54
3k	5,6,7-$(MeO)_3$	Et	55
3l	H	2-(3,4-dimethoxyphenyl)ethyl	74

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Note that only aliphatic amines, which are good nucleophiles, can participate in the transformation. No reaction takes place in the case of anilines and *tert*-butylamine. We have found that **2** bearing both Br and Cl atoms at the double bond can be involved into reaction. No reaction is observed in the case of 1-(2-bromo-3,3,3-trifluoroprop-1-enyl)-2,4-dichlorobenzene giving tar products only.

Thus, we have elaborated a new effective approach to 2-trifluoromethylindoles, which allows preparation of the target product with variation of substituents at benzene ring and nitrogen atom.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2008.11.014.

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† IR spectra were recorded on a UR 20 spectrophotometer (Nujol), all indoles have the signals of CF_3 group in the 1300–1100 cm^{-1} area. ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 spectrometer (400 and 100 MHz, respectively) in $CDCl_3$ with TMS as the internal standard. TLC was carried out with Merck 60 F254 plates; Merck silica gel (63–200) mesh was used for column chromatography.

General procedure for the synthesis of 2-trifluoromethylindoles. 1 mmol of corresponding β-halo-β-(trifluoromethyl)-(*o*-halostyrene), 1.2 mmol of primary amine, 0.019 g (10 mol%) of CuI, 0.414 g (3 mmol) of K_2CO_3 and 2 ml of DMSO were placed to a sealed reactor. The reaction mixture was heated to 90–100 °C and was stirred at this temperature for 18 h. After that it was placed to 50 ml of water, the reaction products were extracted with CH_2Cl_2 (3×20 ml). Organic layer was washed twice by water, brine and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by flash chromatography on SiO_2 using 1:1 hexane–CH_2Cl_2 as an eluent.

*1-Hexyl-2-(trifluoromethyl)-1*H*-indole* **3a**: yellowish oil. ^1H NMR ($CDCl_3$) δ: 1.01 (t, 3H, hexyl, H-6, ^3J 7.0 Hz), 1.39–1.46 (m, 4H, hexyl, H-4,5), 1.48–1.53 (m, 2H, hexyl, H-3), 1.88–1.95 (m, 2H, hexyl, H-2), 4.29 (t, 2H, hexyl, H-1, ^3J 8.1 Hz), 7.02 (s, 1H, H-3), 7.27 (t, 1H, H-5, ^3J 7.3 Hz), 7.42–7.48 (m, 2H, H-6,7), 7.76 (d, 1H, H-4, ^3J 8.1 Hz). ^{13}C NMR ($CDCl_3$) δ: 14.02, 22.62, 26.70, 30.03, 31.46, 45.09 (C_{hexyl}), 104.46 (q, *C*=C–CF_3, ^3J 3.7 Hz), 110.35 ($C_{arom.}$), 120.64 ($C_{arom.}$), 121.73 (q, CF_3, ^1J 268.1 Hz), 122.39, 124.33, 125.95, 126.84 (q, *C*–CF_3, ^2J 37.3 Hz), 137.88 ($C_{arom.}$). Found (%): C, 65.74; H, 7.27. Calc. for $C_{15}H_{18}F_3N{\cdot}0.25H_2O$ (%): C, 65.80; H, 6.81.

Other spectral data are given in the Online Supplementary Materials.

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