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Elaboration of 2-(Trifluoromethyl)indoles via a Cascade Coupling/Condensation/ Deacylation Process

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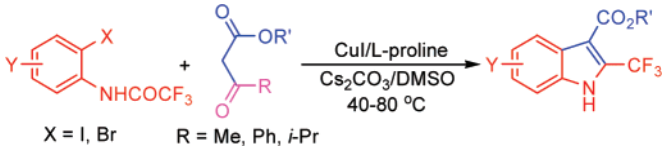
ABSTRACT



CuI/L-proline-catalyzed coupling of 2-halotrifluoroacetanilides with β-keto esters in anhydrous DMSO under the action of Cs_2CO_3 at 40−80 °C produces polysubstituted 2-(trifluoromethyl)indoles in good to excellent yields. This reaction is suggested to occur via a novel coupling/condensation/deacylation mechanism, and many functional groups are tolerated under these conditions.

Substitution of a methyl group or a chlorine atom by a trifluoromethyl group has become a routine operation in drug discovery. This action normally makes the resultant compounds retain their original biological activities but improves the pharmacokinetic properties owing to the unique chemical and physiological stability of this functional group.[1] This fact has stimulated enormous efforts to introduce a trifluoromethyl group into aromatic systems.[2] Indoles with a 2-trifluoromethyl substituent have been widely employed as core structures for developing pharmaceutically important molecules. Recent successful examples include chemokine receptor 5 (CCR5) antagonist **1** (Figure 1),[3] general anesthesia inducer **2**,[4] tyrosine kinase inhibitor **3**,[5] and antitumor compound **4**.[6]

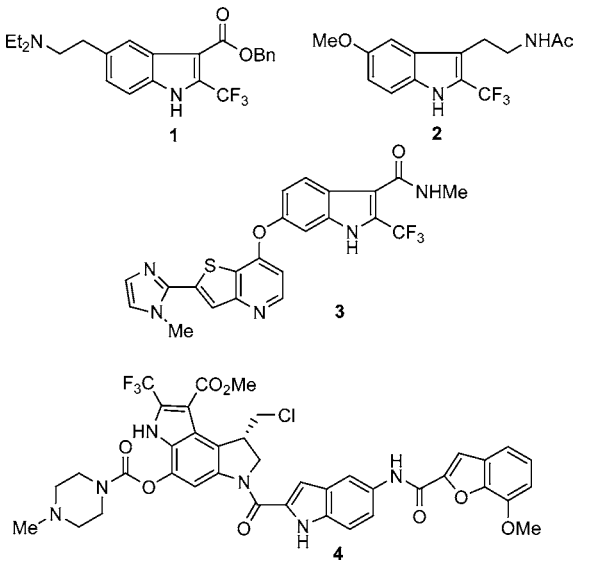


Figure 1. Structures of some pharmaceutically important 2-(trifluoromethyl)indoles.

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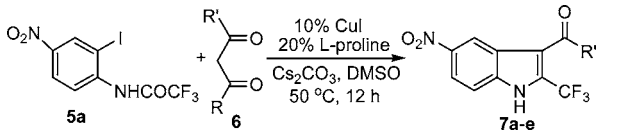
Over the past decades, several methods for the assembly of 2-(trifluoromethyl)indoles have been developed, which include titanium-catalyzed carbonyl coupling of 2-acyltrifluoroacetanilides,[7] PPh_3/TsOH-mediated thermolysis of 2-(*N*-trifluoroacetamino)benzyl methyl ethers,[8] Pd-catalyzed annulation of fluorine-comprising internal alkynes with 2-iodoanilines,[9] as well as the Grignard cyclization reaction of fluorinated *N*-arylimidoyl chlorides.[10] All of these approaches suffer from both the limited availability of the starting materials and of poor yields and regioselectivity. In 1997, Latham and Stanforth reported that 2-(trifluoromethyl)indoles could be synthesized from easily accessible 2-halotrifluoroacetanilides,[11] a method which has been successively applied in the preparation of CCR5 antagonist **1**[3] and tyrosine kinase inhibitor **3**.[5] However, it afforded the desired products only in moderate yields, and a number of steps (enamine formation and Heck reaction) were required.[3,11] Herein, we wish to report a one-step and high-yielding procedure to synthesize 2-(trifluoromethyl)indoles from 2-halotrifluoroacetanilides.

Recently, we revealed that polysubstituted indoles could be prepared from substituted 2-halotrifluoroacetanilides[12] via CuI/L-proline-catalyzed coupling with β-keto esters[13] and subsequent base- or acid-induced hydrolysis.[14] We found that under anhydrous conditions coupling of 4-nitro-2-iodotrifluoroacetanilide (**5a**) with methyl acetoacetate produced 2-(trifluoromethyl)-5-nitroindole (**7a**) in 78% yield (entry 1, Table 1). This undesired transformation prompted us to investigate its general applicability and possible mechanism. Accordingly, different β-keto esters were employed for this process, and it was noticed that each of them gave an indole bearing the ester moiety at its 3-position, the corresponding keto part of the β-keto esters being lost during the course of the reaction (entries 2−7). When diethyl malonate or a β-keto amide were utilized, only simple coupling products were isolated (entries 8 and 9), indicating that a keto moiety is essential for indole formation and the possibility of obtaining indoles with a 3-amide substituent is ruled out.

Table 1. Synthesis of 2-(Trifluoromethyl)-5-nitroindoles via Coupling of 4-Nitro-2-iodotrifluoroacetanilide (**5a**) with β-Keto Esters[a]



entry	R	R′	product	yield[b] (%)
1	Me	MeO	**7a**	78
2	Me	EtO	**7b**	85
3	Me	*t*-BuO	**7c**	81
4	Me	*c*-HexylO	**7d**	80
5	Me	BnO	**7e**	83
6	Ph	EtO	**7b**	78
7	*i*-Pr	MeO	**7a**	84
8	EtO	EtO	*c*	
9	Me	PhNH	*c*	

[a] Reaction conditions: **5a** (0.25 mmol), **6** (0.5 mmol), CuI (0.025 mmol), L-proline (0.05 mmol), Cs_2CO_3 (1.0 mmol), DMSO (0.5 mL), 50 °C, 12 h. [b] Isolated yield. [c] Simple coupling products were isolated in about 64% yield for entry 8 and 78% yield for entry 9.

We then explored the possibility of using other substituted 2-halotrifluoroacetanilides as substrates. The reaction of 2-iodotrifluoroacetanilide (**5b**) with ethyl acetoacetate **6b** gave indole **7f** in only a 27% yield (Table 2, entry 1). In this case, a side product **9** (Scheme 1) was isolated in 54% yield, indicating that after coupling immediate deacylation occurred. Gratifyingly, this side reaction could be suppressed by using sterically hindered β-keto ester **6g** (entry 2). Other substituted 2-iodotrifluoroacetanilides were examined with this keto ester as a coupling partner. Generally, electron-deficient 2-iodotrifluoroacetanilides were more reactive and gave better yields than electron-rich substrates (compare entries 3−5 and 7−9). These results illustrate that the electron-withdrawing groups in the substrates, which render the carbonyl group of the trifluoroacetamide moiety more active, might assist the reaction. This assumption was supported by the remarkably different reactivity of 4-acyl-2-iodotrifluoroacetanilide **5c** and 5-acyl-2-iodotrifluoro-acetanilide (**5f**) (compare entries 3 and 6).

The three diiodides **5i**−**k** reacted smoothly to afford 2,3,5,6- or 2,3,6,7-tetrasubstituted indoles in good yields (entries 9−11); the 5-iodo group could be used for further coupling reactions to obtain more complex indoles. Starting from 4-hydroxyethyl-2-iodotrifluoroacetanilide (**5l**), indole **7q**, which is obviously a promising intermediate for elabora-

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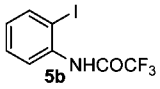
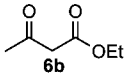
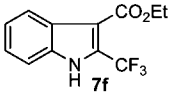
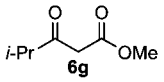
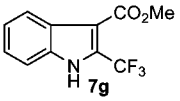
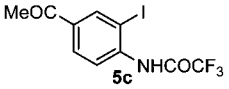
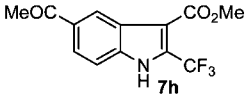
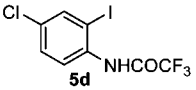
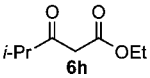
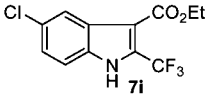
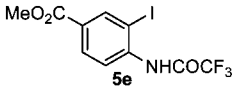
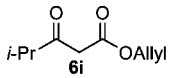
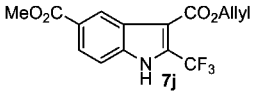
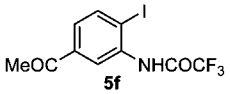
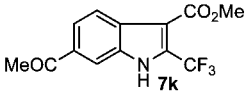
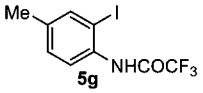
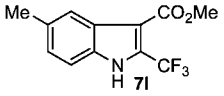
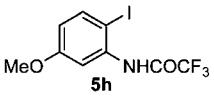
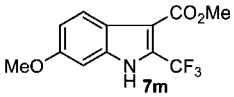
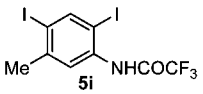
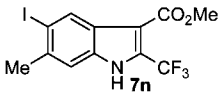
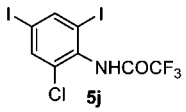
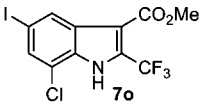
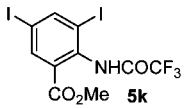
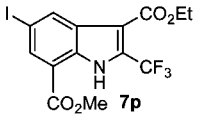
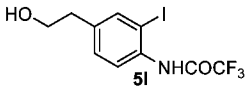
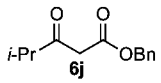
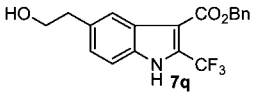
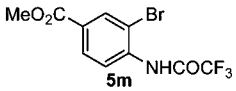
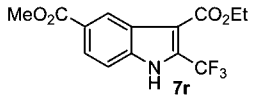
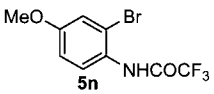
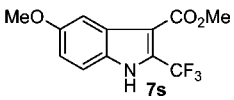
Table 2. Synthesis of 2-(Trifluoromethyl)indoles via Coupling of 2-Halotrifluoroacetanilides **5** with β-Keto Esters[a]

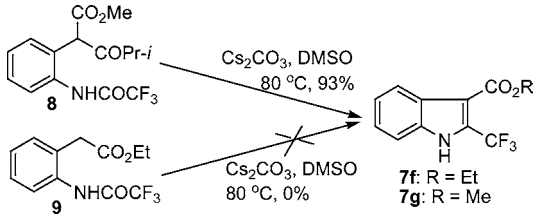
entry	2-halotrifluoroacetanilide	β-keto ester	temp (°C)/time (h)	product	yield (%)[b]
1	 **5b**	 **6b**	80/15	 **7f**	27[c]
2		 **6g**	80/15	 **7g**	80
3	 **5c**	**6g**	60/12	 **7h**	93
4	 **5d**	 **6h**	70/15	 **7i**	81
5	 **5e**	 **6i**	70/15	 **7j**	72
6	 **5f**	**6g**	70/15	 **7k**	65
7	 **5g**	**6g**	70/18	 **7l**	63
8	 **5h**	**6g**	75/15	 **7m**	70
9	 **5i**	**6g**	75/15	 **7n**	79
10	 **5j**	**6g**	60/12	 **7o**	77
11	 **5k**	**6b**	40/12	 **7p**	78
12	 **5l**	 **6j**	80/15	 **7q**	67
13	 **5m**	**6h**	70/15	 **7r**	72[d]
14	 **5n**	**6g**	80/18	 **7s**	55[d]

[a] Reaction conditions: 2-halotrifluoroacetanilides **5** (0.25 mmol), β-keto esters **6** (0.5 mmol), CuI (0.025 mmol), L-proline (0.05 mmol), Cs_2CO_3 (1.0 mmol), DMSO (0.5 mL). [b] Isolated yield. [c] **9** was isolated in 54% yield. [d] CuI (0.05 mmol) and L-proline (0.1 mmol) were used.

tion of CCR5 antagonist **1**,[3] was assembled in a 67% yield (entry 12). When aryl bromides were employed as substrates, increased catalyst loading was required to ensure satisfactory yields (entries 13 and 14). Electron-deficient bromide **5m** showed a higher reactivity than electronic-rich bromide **5n**, which is consistent with the order observed for aryl iodides. Noteworthy is that product **7s** is a possible intermediate for the preparation of anesthesia inducer **2**.[4]

In order to reveal the possible mechanism for the present reaction, compound **8**, the coupling product of **5b** and **6g** at room temperature, was isolated and subsequently treated with Cs_2CO_3 in DMSO at 80 °C. It was found that after 12 h

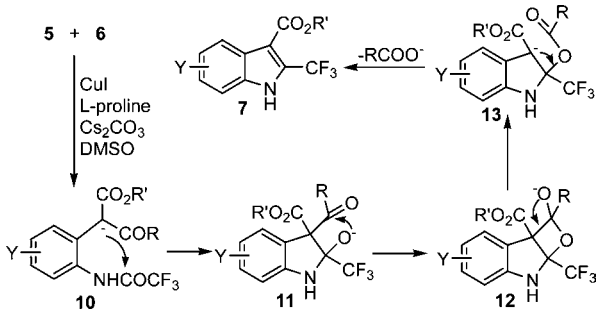
Scheme 1



indole **7g** had formed in 93% yield, while no indole **7f** could be detected when ester **9** was treated under the same conditions (Scheme 1). These results, together with the observation that the reaction of **5a** with diethyl malonate gave only a simple coupling product (entry 8, Table 1), demonstrated clearly that the β-keto group in the coupling product plays a crucial role for the transformation into indoles. Consequently, a possible mechanism to rationalize these results is proposed in Scheme 2. After initial formation of coupling intermediate **10**, the carbanion could attack the carbonyl group of the trifluoroacetamide moiety to produce intermediate **11**. Next, the alkoxy anion in **11** would attack the keto group to form a four-membered ring, in which C−C bond disconnection might occur to yield **13**. Finally, indole **7** could be produced by deacylation of the intermediate **13**.

In conclusion, we have developed a simple and convenient method to convert 2-halotrifluoroacetanilides into 2-(trifluoromethyl)indoles. By varying the substituents of 2-halotrifluoroacetanilides and β-keto esters, a wide range of substituted 2-(trifluoromethyl)indoles have been prepared,

Scheme 2



including two indoles that are useful precursors for known biologically important compounds. This reaction occurs via a novel mechanism, and many functional groups, such as nitro, ketone, ester, hydroxy, iodo, chloro, and olefin, are tolerated under these conditions. Thus, it should be of great benefit for organic synthesis.

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Supporting Information Available: Experimental procedures and copies of ^{1}H NMR and ^{13}C NMR spectra for all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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