RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2020, **10**, 13929

Synthesis of 1-(β-coumarinyl)-1-(β-indolyl) trifluoroethanols through regioselective Friedel–Crafts alkylation of indoles with β-(trifluoroacetyl) coumarins catalyzed by $Sc(OTf)_3$†

Lijun Shi, ‡[a] Ying Liu,‡[a] Caixia Wang,[a] Xinxin Yuan, [b] Xiaobiao Liu,[a] Lulu Wu,[a] Zhenliang Pan,[a] Qicheng Yu,[c] Cuilian Xu*[a] and Guoyu Yang*[a]

Received 8th February 2020
Accepted 20th March 2020

DOI: 10.1039/d0ra01237h

rsc.li/rsc-advances

A highly efficient Friedel–Crafts alkylation of indole derivatives with β-(trifluoroacetyl)coumarins using $Sc(OTf)_3$ as a catalyst has been developed, which gives regioselective 1,2-adducts to afford 1-(β-coumarinyl)-1-(β-indolyl)trifluoroethanols. A series of tertiary trifluoroethanols containing different indole and coumarin groups were synthesized in moderate to excellent yields (up to 95%) in the presence of 5 mol% catalyst in a short time (only 2 minutes at least). A mechanism of the reaction, in which the trace amount of water plays the role of proton transfer in catalyzing circulation was proposed and confirmed.

Introduction

In comparison with their non-fluorinated parent compounds, fluorinated organic compounds often show unique and important physical, chemical, and biological properties due to the strong electron-withdrawing properties, low polarizability and small size of the fluorine atom, and the strength of the C–F bond. Over the last decades, such compounds have been used to great effect in the pharmaceutical and agrochemical industries.[1] Currently, about 20–30% of agrochemicals and pharmaceuticals owe their effectiveness to the presence of one or more fluorine atoms in their structures.[2] In 2018, the U.S. Food and Drug Administration (FDA) approved 38 small molecule drugs and 18 of them contained fluorine.[3] Among the fluorinated groups, the trifluoromethyl motif is of particular interest and this unit is widely used in the quest for new bioactive molecules, as illustrated by the recent marketed molecules.[2a,b] Consequently, a lot of effort has been made to develop an efficient reaction for the synthesis of CF_3-containing compounds over the last decades.[4] For example, α,β-unsaturated trifluoromethyl ketones, possessing a directly linking electron-withdrawing trifluoromethyl group with a highly reactive π-system, have been used in numerous transformations, including hydrogenation,[5] aldol,[6] epoxidation,[7] Michael-type[8] and Diels–Alder reactions[9] to construct trifluoromethylated organic compounds.

On the other hand, the Friedel–Crafts (F–C) alkylation of indoles is of interest because the indole nucleus is widely present in numerous natural products in biological and pharmaceutically compounds.[10] Among them, the conjugate addition of indoles as nucleophiles to α,β-unsaturated carbonyl compounds is very efficient and convenient. In most cases, the addition of indole to α,β-unsaturated ketones yields the corresponding β-indolylketones, including protic acid or Lewis acid-mediated reactions.[11] Until now, most of the available Friedel–Crafts reactions of indoles with α,β-unsaturated carbonyl compounds were limited to 1,4-addition, which can also be considered as a Michael addition of α,β-unsaturated carbonyl compounds with indoles. These α,β-unsaturated carbonyl compounds contains methyl vinyl ketone, acrylic acid, 2-cyclohexen-1-one, ethyl propiolate,[12] α,β-unsaturated aldehydes,[12,13] chalcones,[12,14] α,β-unsaturated trifluoromethyl ketones,[8b] β-trifluoromethyl-α,β-enones,[15] β,γ-unsaturated α-keto esters,[16] α,β-unsaturated 2-acyl imidazoles,[17] methyl 2-acetamidoacrylate,[18] intramolecular α,β-unsaturated carbonyl compounds[19] and so on. To the best of our knowledge, the Friedel–Crafts 1,2-addition of indole with α,β-unsaturated carbonyl compounds to afford an α,β-unsaturated alcohol has not been reported yet, although a Friedel–Crafts alkylation of pyrrole with β,γ-unsaturated α-keto esters was developed to afford the β,γ-unsaturated α-hydroxy esters.[20]

Coumarin-based derivatives also show a wide range of valuable biological activities in medicinal and pharmaceutical areas,[21] such as antimicrobial,[22] anti-inflammatory,[23] antitubercular,[24] anti-osteoporotic,[25] antidiabetic,[26] enzyme inhibitory,[27] anticancer,[28] and antioxidant[23b,29] properties.

[a]School of Science, Henan Agricultural University, Zhengzhou 450002, P. R. China. E-mail: xucuilian666@henau.edu.cn; yangguoyulxy@henau.edu.cn

[b]College of Resource and Environment, Henan Agricultural University, Zhengzhou 450002, P. R. China

[c]College of Animal Science and Veterinary Medicine, Henan Agricultural University, Zhengzhou 450002, P. R. China

† Electronic supplementary information (ESI) available. CCDC 1950379 and 1950380. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0ra01237h

‡ These two authors contributed equally to this work.

Various fluoro-substituted coumarins have been recently reported.[30] We recently developed an efficient method to prepare β-(trifluoromethyl)coumarins (**1**), being a particular α,β-unsaturated carbonyl system and containing diverse functionality, by direct transformation of ethyl 2-hydroxy-2-trifluoromethyl-2*H*-chromene-3-carboxylates under microwave assisted solvent-free conditions.[31] Various trifluoromethyl coumarin thiosemicarbazones and hydrozones were synthesized from ketones **1** and showed excellent antifungal activities.[32] Considering the above reports, and as part of our program aimed at developing new methodologies for the preparation of coumarin derivatives with biological activities, we planned to explore the reaction of compound **1** with indoles to prepare novel coumarin derivatives with trifluoromethyl group and indole scaffold.

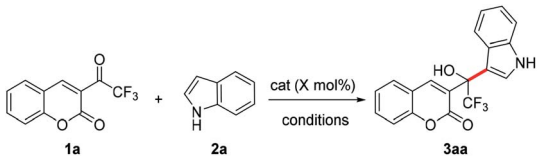
Here, we report the first synthesis of 1-(β-coumarinyl)-1-(β-indolyl)trifluoroethanols through an addition of β-(trifluoroacetyl) coumarin **1** using $Sc(OTf)_3$ as a catalyst. Different from our previous work,[32] which was a 1,4-addition, this work is a regioselective synthesis through 1,2- addition (Scheme 1).

Results and discussion

To examine this proposed addition, we started to explore the practicability of this transformation, and chose the reaction of β-(trifluoroacetyl)coumarin **1a** with indole **2a** as the model (Table 1. For more details, see Table S1 in ESI†).

Based on similar previous studies, which showed that Lewis acid or protic acid could promote the conjugation addition of indole to α,β-unsaturated ketones, the reaction was initially carried out in the presence of different Lewis acids or protic acids in CH_2Cl_2 (dichloromethane) at 25 °C for 2 hours. Lewis acids, containing $AlCl_3$, $FeCl_3$, $Pb(OAc)_2$, $Cu(OTf)_2$, $Fe(OTf)_3$, $Y(OTf)_3$, and protic acids, containing *p*-toluenesulfonic acid (*p*-TSA), trifluoromethanesulfonyl acid (TfOH) were previously studied as catalysts. However, only a trace or a small amount of adduct **3aa** was obtained (entries 2–5, Table 1 or entries 2–9, Table S1 in ESI†). To our delight, $Sc(OTf)_3$ could catalyze the carbonyl addition quite effectively and gave **3aa** in 93% yield (entry 6, Table 1). The yield increased to 95% when the reaction time was extended to 5 hours, and only decreased a little when the reaction time was reduced to 30 min. By screening solvents, we found that moderate polar solvents such as CH_2Cl_2 and $CHCl_3$, weak and nonpolar solvents like toluene, 1,2-dichloroethane and CCl_4, worked better than polar solvents (CH_3CN, EtOH and HOAc) for the reaction, and CH_2Cl_2 produced the best satisfactory results (entries 6–13, Table 1). Apart from the above-mentioned factors, the effects of reaction temperature, the amount of catalyst, the ratio of the reactants and the moisture were also investigated (entries 14–20, Table 1). The optimal reaction conditions were determined to be under reflux (45 °C) for 20 min in air atmosphere, with addition of 5% $Sc(OTf)_3$ as catalyst, CH_2Cl_2 as solvent and 1 : 1 of the ratio **1a** : **2a** (entry 14, Table 1).

Table 1 Optimization of reaction conditions[a]

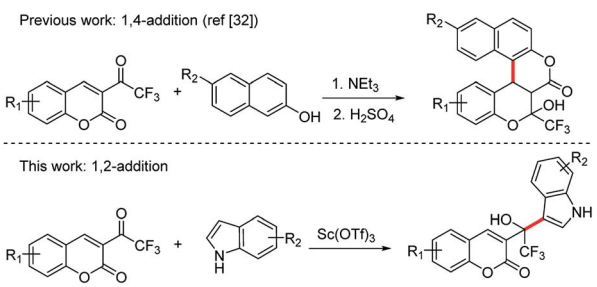


Entry	Catalyst	*X*	Solvent	*T*/°C	Time[b]/min	Yield[c]/%
1	None	—	CH_2Cl_2	25	120	N. R.
2	$AlCl_3$	5	CH_2Cl_2	25	120	15
3	$Fe(OTf)_3$	5	CH_2Cl_2	25	120	25
4	$Y(OTf)_3$	5	CH_2Cl_2	25	120	45
5	TfOH	5	CH_2Cl_2	25	120	8
6	$Sc(OTf)_3$	5	CH_2Cl_2	25	120	93
7	$Sc(OTf)_3$	5	$CHCl_3$	25	120	90
8	$Sc(OTf)_3$	5	CCl_4	25	120	87
9	$Sc(OTf)_3$	5	DCE	25	120	82
10	$Sc(OTf)_3$	5	Toluene	25	120	75
11	$Sc(OTf)_3$	5	CH_3CN	25	120	38
12	$Sc(OTf)_3$	5	EtOH	25	120	72
13	$Sc(OTf)_3$	5	HOAc	25	120	65
14	**$Sc(OTf)_3$**	**5**	**CH_2Cl_2**	**Reflux**	**20**	**95**
15	$Sc(OTf)_3$	5	CH_2Cl_2	Reflux	30	92
16	$Sc(OTf)_3$	5	CH_2Cl_2	Reflux	90	88
17	$Sc(OTf)_3$	7.5	CH_2Cl_2	Reflux	30	91
18	$Sc(OTf)_3$	10	CH_2Cl_2	Reflux	30	90
19[d]	$Sc(OTf)_3$	5	CH_2Cl_2	Reflux	60	61
20[e]	$Sc(OTf)_3$	5	CH_2Cl_2	Reflux	20	92

[a] The reactions were performed on a 0.2 mmol scale using **1a** (1.0 equiv.) and **2a** (1.0 equiv. in entries 1–19; 1.1 equiv. in entry 20) in 2.0 mL of solvent under air atmosphere. The reactants, catalysts and solvents were used without further treatment (except entries 19). [b] The reactions were monitored by HPLC analysis using a ^{18}C chromatographic column. Mobile phase was MeOH : H_2O = 75% : 25% and flow velocity was 1.0 mL min^{-1}. [c] Isolated yield. [d] The ratio of **1a** : **2a** = 1 : 1.1. [e] The reactants and catalyst (**1a**, **2a** and $Sc(OTf)_3$) were dried under vacuum at room temperature in a desiccator for 2 hours to remove moisture. The solvent (CH_2Cl_2) was distilled over phosphorus pentoxide.

With the promising results obtained in the model reaction, we subsequently examined the substrate scope of the transformation. The results of 27 examples are summarized in Table 2. The reactions were monitored by HPLC. The reaction time and corresponding isolated yields were shown in the Table 2.

All tested substituted indoles **2a–h** reacted with β-(trifluoromethyl) coumarins **1a–f** and gave the 1-(β-coumarinyl)-1-(β-indolyl)-trifluoroethanols **3aa–3fa** in high to excellent



Scheme 1 1,4-Addition and 1,2-addition of β-(trifluoroacetyl) coumarins.

isolated yields (72% to 95%, Table 2). Of note, all the reactions proceeded smoothly and completed in less than 2 hours, and the conditions were tolerant to different substituents. The electronic nature of aromatic ring of coumarins has little influence on the yield of the reactions (**3ba**, **3ca**, **3da**, **3ea** and **3fa**).

The indole ring, which was connected with an electron-donating group (such as methyl or methoxyl), was advantageous to reaction rate (**3ab**, **3ac**, **3ae**, **3af** and **3eb**, **3ec**, **3ee**, **3ef**). The addition was completed in 2 minutes at least. However, in the case of 4- benzyloxyindole (**2d**), the reaction time was longer than 4-methyloxyindole (**2c**), such as **3ac** and **3ad**, **3bc** and **3bd**, **3cc** and **3cd**, **3dc** and **3dd**, **3ec** and **3ed**, which was perhaps due to the steric effect of benzyloxyl. When an electron-withdrawing group was attached to the indole ring, such as 5-chloroindole (**2g**) or 6-bromoindole (**2h**), the reaction became slower obviously (**3ag**, **3ah** and **3eh**).

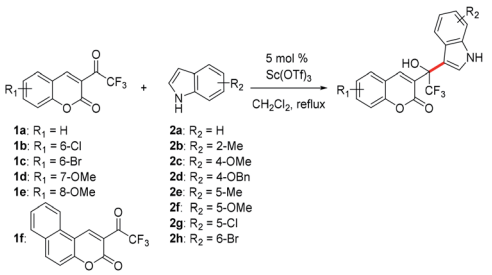
It was similar to coumarins' phenyl ring. Especially, when 8-methoxyl-3-(trifluoroacetyl)coumarin (**1e**) reacted with 4-benzyloxyindole (**2d**), the reaction time was reduced from 50 to 16 minutes in contrast to the reaction of **1a** with **2d**. On the contrary, when coumarins' phenyl ring was connected with an electron-withdrawing group, such as a chlorine or bromine atom (**1b** and **1c**), the reactions all slowed down (**3ba**, **3bc**, **3bd** and **3ca**, **3cd**, **3ce**).

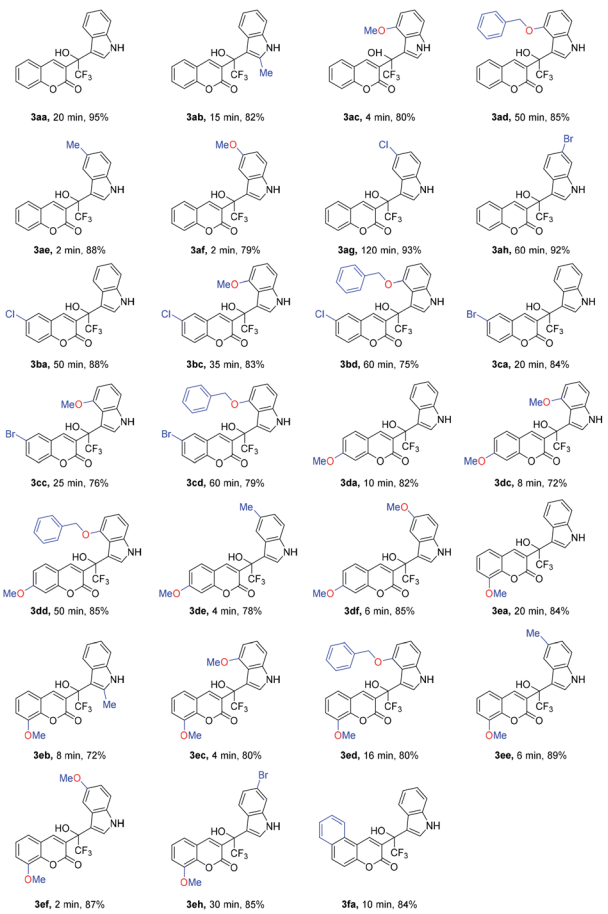
When benzo[*f*]coumarin (**1f**) was used instead, the reaction rate became higher than that of **1a**, because the larger conjugate system increased electron cloud density of coumarin.

The structures of compound **3aa–3fa** were confirmed by ^{1}H NMR, ^{13}C NMR and HRMS spectroscopy. All ^{1}H and ^{13}C NMR spectra used d_6-DMSO as a solvent to avoid the interference of peaks from residual non-deuterium solvent. A ^{1}H–^{13}C COSY spectrum of **3aa** and ^{1}H NMR spectrum of **3aa** exchanged by D_2O were also given as additional information to confirm the ownership of every signal in ^{1}H NMR and ^{13}C NMR. The ^{1}H–^{13}C COSY spectrum showed that there were only two hydrogens which did not attach to a carbon. In the ^{1}H NMR spectrum of **3aa**, these two signals were observed at δ 11.30 ppm and 7.34 ppm which belonged to the indole NH and tertiary alcohol OH respectively, and the integral areas decreased from 1.00 to 0.69 and 0.18 after D_2O exchanged for 2 hours (See Fig. S3 in ESI†). Ten aromatic protons appeared in the range of δ 6.87–8.69 ppm. In the ^{13}C NMR spectrum of **3aa**, the lactone carbonyl carbon appeared at δ 157.46 ppm, while the carbon atom attached to the oxygen in the coumarin ring was observed at δ 153.55 ppm. The carbon of CF_3 and the carbon attached to the hydroxyl and CF_3 with their corresponding coupling constants $J_{C,F} = 287.9$ Hz and 30.0 Hz, appeared as a quartet at δ 125.47 and 74.49 ppm, respectively. Compared with spectrum of **1a** and **2a** and fitted by ChemDraw software, the ownerships of other signals of **3aa** in ^{1}H NMR and ^{13}C NMR are shown in the ^{1}H–^{13}C COSY spectrum (See Fig. S7 in ESI†). In the ^{19}F NMR spectrum of **3aa**, only a singlet was observed at δ −74.21 ppm which belongs to the three fluorine atoms of CF_3. Compounds **3ab–3fa** showed the similar signals in ^{1}H and ^{13}C NMR. Compounds **3aa–3fa** all showed the molecular-ion peak [M − H]$^+$ or [M + H]$^+$ in the high resolution mass spectrum, matching with the calculated data.

The structures of coumarin derivatives were further confirmed by the X-ray diffraction determination of single crystals of compounds **3aa** and **3dd** (single crystal X-ray diffraction data of compounds **3aa** and **3dd** are deposited with CCDC No. 1950379 and 1950380, respectively). The perspective and packing views are shown in Fig. 1 and 2 respectively. The crystal data and refinement details are given in

Table 2 Sc(OTf)$_3$-catalyzed addition of indoles **2a–h** with **1a–f**[a]





[a] The reactions were carried out with **1a–f** and **2a–f** on a 0.2 mmol scale in 2.0 mL CH_2Cl_2 under reflux (45 °C) in air atmosphere, and monitored by HPLC analysis using a ^{18}C chromatographic column. Mobile phase was MeOH : H_2O = 75% : 25% and flow velocity was 1.0 mL min^{-1}. The yield was given as isolated yield.

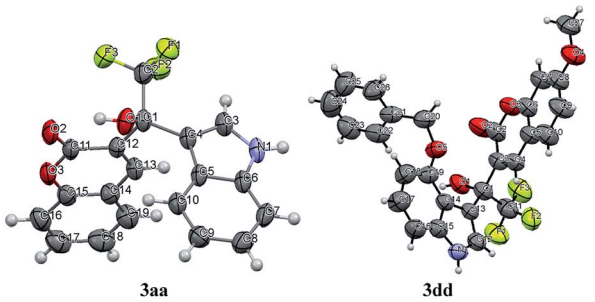
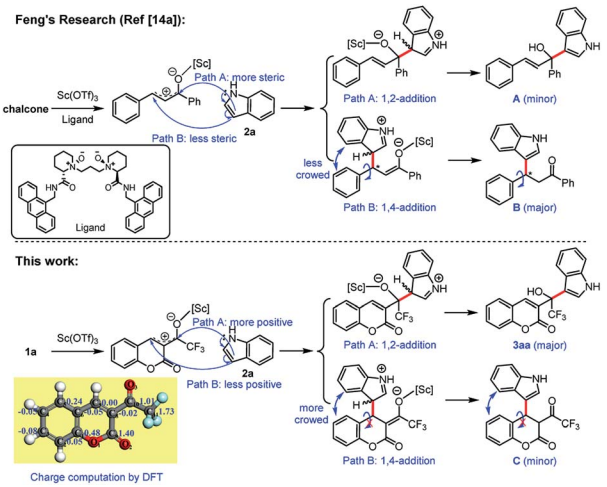


Fig. 1 X-ray structures of products **3aa** and **3dd**.

Tables S2–S15 in ESI.† It is seen that compounds **3aa** and **3dd** are isomorphous, and they crystallize in the monoclinic space $P2_1/c$ and $C2/c$ respectively with four molecules in the unit cell.

In the crystal structure of **3dd**, we can see that the C–O bond between C20 and O5 could not rotate freely because of the steric effect of coumarin group. In ^{1}H NMR spectrum of **3dd**, the two benzyl hydrogens showed two signals at δ 5.04 and 4.93 ppm, which means they are magnetic nonequivalent. Each hydrogen shows a doublet with a coupling constant $J = 12.9$ Hz from each other. Similar signals were found in ^{1}H NMR spectrum of other products of **2d**, such as **3ad**, **3bd**, **3cd** and **3ed**.

The reaction was 1,2-addition instead of 1,4-addition which was confirmed by the crystal structures of the adducts of the Friedel–Crafts alkylation of indoles **2** with β-(trifluoroacetyl) coumarins **1** catalyzed by $Sc(OTf)_3$. We attributed the main reason to the steric effect in the intermediate. Here, we compares the addition of chalcone which has a similar phenyl α,β-unsaturated ketone with **1a** (see Scheme 2). In the carbocation formed by **1a** in the present of $Sc(OTf)_3$, the carbon next to the trifluoromethyl was more positive than the 4-carbon of the coumarin ring, which was confirmed by the charge computation of density functional theory (DFT). However, only the electronic property was not enough and it still tended to give the 1,4-adduct through Michael-type addition (see examples for 1,4-addition of α,β-unsaturated trifluoromethyl ketones with indoles in ref. 8*b*). We supposed that in the 1,4-adduct **B** formed by chalcone and indole **2a**, the C–C bond between the phenyl and new tertiary carbon could rotate freely. By contrast, in the 1,4-adduct **C** from **1a** and indole **2a**, the C–C bond between the phenyl and new tertiary carbon could not rotate at all, because of the rigid structure of coumarin ring. Thus the indolyl and coumarinyl groups were very crowd in the 1,4-adduct **C** which



Scheme 2 Comparison between additions of chalcone and **1a** with indole **2a**.

was a minor adduct. In fact, only 1,2-adduct **3aa** was observed in this reaction.

According to the result of above analysis, a proposed mechanism of 1,2-addition of **1a** and **2a** is shown in Scheme 3. It should be noted that a little water in the solution played the role of transmitting protons, and the reaction could be completed in a very short time (2–120 minutes). The water might come from the solvent which was used without any treatment, and β-(trifluoroacetyl)coumarins **1** which has a very electron-deficient carbonyl and can exist as a hydrate easily (see the crystal structure of hydrate of **1a** in ref. 31*b* or CCDC 967230). Through the DFT computation, Yu *et al.* discovered that a trace amount of water could play a role of proton transfer in catalyzing circulation.[33] By contrast, a reaction of **1a** and **2a** with $Sc(OTf)_3$, which were dried under vacuum at room temperature in a desiccator for 2 hours to remove moisture, in CH_2Cl_2 distilled over phosphorus pentoxide was carried on (see entries 33–35, Table S1†). With less water, the reaction slowed down evidently. After 10 minutes, the yield was only 20%. Even after 1 hour, only 61% of product was obtained. Without any treatment, the reaction could be completed in 20 minutes with a 95% yield.

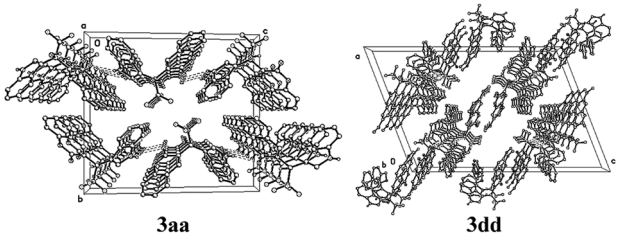
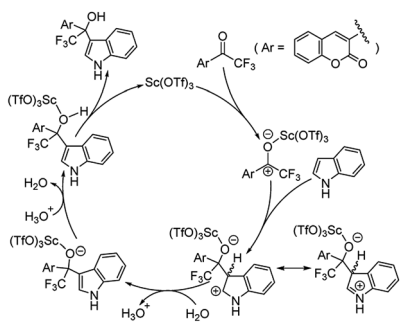


Fig. 2 View of the molecular packings in **3aa** and **3dd**.



Scheme 3 Proposed mechanism of addition of **1a** and **2a**.

Conclusions

In conclusion, we have shown that Friedel–Crafts alkylation of indole derivatives with kinds of β-(trifluoroacetyl)coumarins can be effectively catalyzed by $Sc(OTf)_3$. The reaction proceeds with good yields (up to 95%) in a short time (only 2–120 minutes) and gives 1,2-adducts to afford 1-(β-coumarinyl)-1-(β-indolyl)trifluoroethanols. The conditions are of application to a large number of substituted indoles and β-(trifluoroacetyl) coumarins.

Experimental

General

All solvents and reagents used are commercially available and were used without further purification unless noted. All ^{1}H and ^{13}C NMR spectra used d_6-DMSO as a solvent to avoid the interference of peaks from residual non-deuterium solvent. The NMR data were obtained on a Bruker DPX-400 or 500 Spectrometer, respectively. The MestReNova Software was used to deal with the NMR spectra. Chemical shifts (δ) are reported in ppm and J values are given in hertz. In ^{1}H NMR, the signal of TMS was set as 0.00 ppm unless noted. In ^{13}C NMR, the middle signal of d_6-DMSO was set as 39.60 ppm. All the signals represent 1H or 1C except as noted. HPLC analyses for the qualitative and quantitative analysis of the products were carried out using an Agilent 1200 pump equipped with an Agilent 1200 detector. Melting points were determined on an X-5 digital microscopic melting-point apparatus (Beijing Tech Instruments Co., Beijing, China) and are uncorrected. High resolution mass spectrometry were obtained using a Waters Q-Tof MicroTM instrument. X-ray crystallography parameters for data collection and refinement of the compounds are summarized in Table S1 in ESI.† Intensities were collected on a Rigaku Saturn 724 CCD diffractometer (Mo-Kα, λ = 0.71073 Å) at a temperature of 293 K using the SMART and SAINT programs. The structures were solved by direct method and refined on F2 by full-matrix least-squares methods with SHELXTL-97 crystallographic software package. All the non-hydrogen atoms were refined with anisotropic thermal displacement coefficients. The hydrogen atoms were assigned with common isotropic displacement factors and included in the final refinement by using geometrical restrains.

Preparation of β-(trifluoroacetyl)coumarins 1a–f

β-(Trifluoroacetyl)coumarins **1a–f** were prepared according the microwave assisted solvent-free route *via* Knoevenagel condensation of substituted salicylaldehydes with ethyl trifluoroacetoacetate in the presence of silica-immobilized L-proline and subsequently rearrangement (see ref. 31).

Indole **2a** and substituted indoles **2b–h** were used commercially.

Preparation of 1-(β-coumarinyl)-1-(β-indolyl)trifluoroethanols 3aa–3fa

In a typical experiment of Friedel–Crafts alkylation of indoles, a solution of β-(trifluoroacetyl)coumarin **1a** (0.2 mmol), indole **2a** (0.2 mmol) and $Sc(OTf)_3$ (0.01 mmol, 5% equiv.) in 2 mL CH_2Cl_2 was stirred under atmosphere at 45 °C for 20 minutes. The reaction was monitored by HPLC. When the reaction completed, the mixture was washed by water (5 mL × 3). Then the water phase was extracted by CH_2Cl_2 (5 mL × 3). The combined solution was evaporated under reduced pressure. The crude product was recrystallized from ethyl acetate and petroleum ether (1 : 10), to afford the product **3aa** as a light yellow powder (95% yield).

Characterization data of new compounds

Representative example **3aa** is given below; for other compounds (**3ab–3fa**), see the ESI.†

1-(Coumarin-3-yl)-1-(1*H*-indol-3-yl)-2,2,2-trifluoroethanol (3aa). Yield 95%, light yellow powder, mp 244.6–244.9 °C. ^{1}H NMR (400 MHz) δ 11.30 (s, N*H*), 8.69 (s), 7.99 (d, J = 7.4 Hz), 7.64 (t, J = 7.6 Hz), 7.48 (s), 7.44–7.34 (m, 5H), 7.07 (t, J = 7.5 Hz), 6.89 (t, J = 7.5 Hz). ^{13}C NMR (101 MHz) δ 157.46(*C*=O), 153.55(*C*–O), 143.05, 136.30, 132.73, 129.68, 125.47 (q, J = 287.9 Hz, *C*F_3), 125.39, 125.34, 124.80, 124.37, 121.28, 119.65, 119.12, 118.42, 115.87, 111.91, 110.40, 74.49 (q, J = 30.0 Hz, *C*–CF_3). ^{19}F NMR (376 MHz) δ −74.21 (s, 3F, C*F*$_3$). HRMS: *m/z* calcd for $C_{19}H_{11}F_3NO_3$: 358.0691 $[M - H]^+$; found: 358.0689.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

This work was supported by the Science and Technology Agency of Henan Province (152102110070, 192102110055) and Guidance Program for Key Scientific Research Items of Higher Education of Henan Province (19B210004, 20B150008).

Notes and references

1 For reviews, see:(*a*) R. Filler and Y. Kobayashi, *Biomedicinal Aspects of Fluorine Chemistry*, Elsevier, Amsterdam, 1982; (*b*) J. T. Welch and S. Eswarakrishman, *Fluorine in Bioorganic Chemistry*, Wiley, New York, 1991; (*c*) A. Becker, *Inventory of Industrial Fluoro-Biochemicals*, Eyrolles, Paris, 1996; (*d*) J.-P. Begue and D. Bonnet-Delpon, *Bioorganic and Medicinal Chemistry of Fluorine*, Wiley, Hoboken, 2008; (*e*) S. Purser, P. R. Moore, S. Swallowb and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320–330; (*f*) I. Ojima, *Fluorine in Medicinal Chemistry and Chemical Biology*, Wiley, Chichester, 2009; (*g*) S. Swallow, Fluorine in Medicinal Chemistry (Chapter 2), *Progress in Medicinal Chemistry*, Elsevier, 2015, vol. 54, pp. 65−133.

2 For reviews, see:(*a*) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432–2506; (*b*) B. C. Wang, L. J. Wang, B. Jiang, S. Y. Wang, N. Wu, X. Q. Li and D. Y. Shi, *Mini-Rev. Med. Chem.*, 2017, **17**, 683–692; (*c*) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly

and N. A. Meanwell, *J. Med. Chem.*, 2015, **58**, 8315–8359; (*d*) N. A. Meanwell, *J. Med. Chem.*, 2018, **61**, 5822–5880; (*e*) A. Burriss, A. J. F. Edmunds, D. Emery, R. G. Hall, O. Jacob and J. Schaetzer, *Pest Manage. Sci.*, 2018, **74**, 1228–1238; (*f*) E. Carbonnel, T. Poisson, P. Jubault, X. Pannecoucke and T. Besset, *Front. Chem.*, 2019, **7**, 111.

3 Y. Pan, *ACS Med. Chem. Lett.*, 2019, **10**, 1016–1019.

4 For reviews, see:(*a*) J. A. Ma and D. Cahard, *Chem. Rev.*, 2004, **104**, 6119–6146; (*b*) J. Nie, H. C. Guo, D. Cahard and J. A. Ma, *Chem. Rev.*, 2011, **111**, 455–529; (*c*) X. Y. Yang, T. Wu, R. J. Phipps and F. D. Toste, *Chem. Rev.*, 2015, **115**, 826–870.

5 V. G. Nenajdenko, K. I. Smolko and E. S. Balenkova, *Tetrahedron: Asymmetry*, 2001, **12**, 1259–1266.

6 (*a*) X.-J. Wang, Y. Zhao and J.-T. Liu, *Org. Lett.*, 2007, **9**, 1343–1345; (*b*) D. H. Zhang and C. Y. Yuan, *Tetrahedron*, 2008, **64**, 2480–2488; (*c*) Y.-H. Deng, J.-Q. Chen, L. He, T.-R. Kang, Q.-Z. Liu, S.-W. Luo and W.-C. Yuan, *Chem. - Eur. J.*, 2013, **19**, 7143–7150; (*d*) J. D. Duan, Y. Y. Cheng, J. Cheng, R. Li and P. F. Li, *Chem. - Eur. J.*, 2017, **23**, 519–523.

7 C. Zheng, Y. Li, Y. Yang, H. Wang, H. Cui, J. Zhang and G. Zhao, *Adv. Synth. Catal.*, 2009, **351**, 1685–1691.

8 (*a*) X.-J. Wang, Y. Zhao and J.-T. Liu, *Synthesis*, 2008, 3967–3973; (*b*) S. Sasaki, T. Yamauchi and K. Higashiyama, *Tetrahedron Lett.*, 2010, **51**, 2326–2328; (*c*) Z.-K. Pei, Y. Zheng, J. Nie and J.-A. Ma, *Tetrahedron Lett.*, 2010, **51**, 4658–4661; (*d*) J. Hernández-Toribio, R. G. Arrayás, B. Martín-Matute and J. C. Carretero, *Org. Lett.*, 2009, **11**, 393–396; (*e*) P. Li, Z. Chai, S.-L. Zhao, Y.-Q. Yang, H.-F. Wang, C.-W. Zheng, Y.-P. Cai, G. Zhao and S.-Z. Zhu, *Chem. Commun.*, 2009, 7369–7371; (*f*) X.-K. Chen, C.-W. Zheng, S.-L. Zhao, Z. Chai, Y. Q. Yang, G. Zhao and W.-G. Cao, *Adv. Synth. Catal.*, 2010, **352**, 1648–1652; (*g*) A. Sanz-Marco, G. Blay, M. C. Muñoz and J. R. Pedro, *Chem. Commun.*, 2015, **51**, 8958–8961.

9 (*a*) L. C. Morrill, J. Douglas, T. Lebl, A. M. Z. Slawin, D. J. Fox and A. D. Smith, *Chem. Sci.*, 2013, **4**, 4146–4155; (*b*) A. T. Davies, P. M. Pickett, A. M. Z. Slawin and A. D. Smith, *ACS Catal.*, 2014, **4**, 2696–2700; (*c*) L. C. Morrill, L. A. Ledingham, J.-P. Couturier, J. Bickel, A. D. Harper, C. Fallan and A. D. Smith, *Org. Biomol. Chem.*, 2014, **12**, 624–636; (*d*) R. Mose, M. E. Jensen, G. Preegel and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2015, **54**, 13630–13634; (*e*) Y.-J. Lin, L.-N. Du, T.-R. Kang, Q.-Z. Liu, Z.-Q. Chen and L. He, *Chem. - Eur. J.*, 2015, **21**, 11773–11778; (*f*) N. Attaba, J. E. Taylor, A. M. Z. Slawin and A. D. Smith, *J. Org. Chem.*, 2015, **80**, 9728–9739.

10 For reviews, see: (*a*) R. J. Sundberg, *The Chemistry of Indoles*. Academic. New York, 1996; (*b*) A.-U. Rahman and A. Basha, *Indole Alkaloids*. Harwood Academic, Amsterdam, 1998; (*c*) G. R. Humphrey and J. T. Kuethe, *Chem. Rev.*, 2006, **106**, 2875–2911; (*d*) K. S. Ryan and C. L. Drennan, *Chem. Biol.*, 2009, **16**, 351–364; (*e*) M. Ishikura and K. Yamada, *Nat. Prod. Rep.*, 2009, **26**, 803–852; (*f*) M. Ishikura, K. Yamada and T. Abe, *Nat. Prod. Rep.*, 2010, **27**, 1630–1680; (*g*) N. K. Kaushik, N. Kaushik, P. Attri, N. Kumar, C. H. Kim, A. K. Verma and E. H. Choi, *Molecules*, 2013, **18**, 6620–6662; (*h*) T. V. Sravanthi and S. L. Manju, Indoles—A promising scaffold for drug development, *Eur. J. Pharm. Sci.*, 2016, **91**, 1–10; (*i*) N. Chadha and O. Silakari, *Eur. J. Med. Chem.*, 2017, **134**, 159–184.

11 For reviews, see:(*a*) T. B. Poulsen and K. A. Jørgensen, *Chem. Rev.*, 2008, **108**, 2903–2915; (*b*) S. L. You, Q. Cai and M. Zeng, *Chem. Soc. Rev.*, 2009, **38**, 2190–2201; (*c*) H. Wu, Y. P. He and F. Shi, *Synthesis*, 2015, **47**, 1990–2016; (*d*) V. Pirovano, *Eur. J. Org. Chem.*, 2018, **17**, 1925–1945; (*e*) J. B. Chen and Y. X. Jia, *Org. Biomol. Chem.*, 2017, **15**, 3550–3567.

12 Z. G. Li, Z. J. Shi and C. He, *J. Organomet. Chem.*, 2005, **690**, 5049–5054.

13 (*a*) S.-G. Kim, *Bull. Korean Chem. Soc.*, 2009, **30**, 2519; (*b*) S. B. Jin, C. G. Li, Y. H. Ma, Y. H. Kan, Y. J. Zhang and W. B. Zhang, *Org. Biomol. Chem.*, 2010, **8**, 4011–4015; (*c*) M. Ueda, Y. Yagyu and I. Ryu, *Tetrahedron: Asymmetry*, 2017, **28**, 1070–1077.

14 (*a*) W. T. Wang, X. H. Liu, W. D. Cao, J. Wang, L. L. Lin and X. M. Feng, *Chem. - Eur. J.*, 2010, **16**, 1664–1669; (*b*) T. Narumi, S. Tsuzuki and H. Tamamura, *Asian J. Org. Chem.*, 2014, **3**, 497–503.

15 (*a*) G. Blay, I. Fernández, M. C. Muñoz, J. R. Pedro and C. Vila, *Chem. - Eur. J.*, 2010, **16**, 9117–9122; (*b*) B. Chaudhary, M. Diwakera and S. Sharma, *Org. Chem. Front.*, 2018, **5**, 3133–3137.

16 N. K. Li, L. P. Kong, Z. H. Qi, S. J. Yin, J. Q. Zhang, B. Wu and X. W. Wang, *Adv. Synth. Catal.*, 2016, **358**, 3100–3112.

17 (*a*) H. H. Huo, C. Fu, K. Harms and E. Meggers, *J. Am. Chem. Soc.*, 2014, **136**, 2990–2993; (*b*) S.-W. Li, Q. Wan and Q. Kang, *Org. Lett.*, 2018, **20**, 1312–1315.

18 (*a*) E. Angelini, C. Balsamini, F. Bartoccini, S. Lucarini and G. Piersanti, *J. Org. Chem.*, 2008, **73**, 5654; (*b*) V. Pirovano, D. Facoetti, M. Dell'Acqua, E. D. Fontana, G. Abbiati and E. Rossi, *Org. Lett.*, 2013, **15**, 3812–3815.

19 (*a*) C.-F. Li, H. Liu, J. Liao, Y.-J. Cao, X.-P. Liu and W.-J. Xiao, *Org. Lett.*, 2007, **9**, 1847–1850; (*b*) H. H. Butani, D. D. Vachhani, U. C. Bhoya, A. K. Shah and E. V. Van der Eycken, *Eur. J. Org. Chem.*, 2015, **2015**, 2124–2128.

20 J. N. Sun, Y. B. Hu, Y. N. Li, S. Zhang, Z. G. Zha and Z. Y. Wang, *J. Org. Chem.*, 2017, **82**, 5102–5110.

21 For reviews, see:(*a*) X.-M. Peng, G. L. V. Damu and C.-H. Zhou, *Curr. Pharm. Des.*, 2013, **19**, 3884–3930; (*b*) S. Sandhu, Y. Bansal, O. Silakari and G. Bansal, *Bioorg. Med. Chem.*, 2014, **22**, 3806–3814; (*c*) H. Singh, J. V. Singh, K. Bhagat, H. K. Gulati, M. Sanduja, N. Kumar, N. Kinarivala and S. Sharma, *Bioorg. Med. Chem.*, 2019, **27**, 3477–3510.

22 (*a*) R. Kenchappa, Y. D. Bodke, A. Chandrashekar, S. Telkar, K. S. Manjunatha and M. A. Sindhe, *Arabian J. Chem.*, 2017, **10**, S1336–S1344; (*b*) H. Osman, S. K. Yusufzai, M. S. Khan, B. M. Abd Razik, O. Sulaiman, S. Mohamad, J. A. Gansau, M. O. Ezzat, T. Parumasivam and M. Z. Hassan, *J. Mol. Struct.*, 2018, **1166**, 147–154; (*c*) For a review of coumarins as antiviral agents, see: M. Z. Hassan, H. Osman, M. A. Ali and M. J. Ahsan, *Eur. J. Med. Chem.*, 2016, **123**, 236–255.

23 (*a*) G. Melagraki, A. Afantitis, O. Igglessi-Markopoulou, A. Detsi, M. Koufaki, C. Kontogiorgis and D. J. Hadjipavlou-Litina, *Eur. J. Med. Chem.*, 2009, **44**,

3020–3026; (*b*) R. K. Arora, N. Kaur, Y. Bansaln and G. Bansal, *Acta Pharm. Sin. B*, 2014, **4**, 368–375.

24 C. Fang, K. K. Lee, R. Nietupski, R. H. Bates, R. Fernandez-Menendez, E. M. Lopez-Roman, L. Guijarro-Lopez, Y. X. Yin, Z. Z. Peng, J. E. Gomez, S. Fisher, D. Barros-Aguirre, B. K. Hubbard, M. H. Serrano-Wu and D. T. Hung, *Bioorg. Med. Chem. Lett.*, 2018, **28**, 3529–3533.

25 K. V. Sashidhara, R. K. Modukuri, D. Choudhary, K. B. Rao, M. Kumar, V. Khedgikar and R. Trivedi, *Eur. J. Med. Chem.*, 2013, **70**, 802–810.

26 For a review, see: H. B. Li, Y. F. Yao and L. H. Li, *J. Pharm. Pharmacol.*, 2017, **69**, 1253–1264.

27 (*a*) B.-F. Ruan, H.-J. Cheng, J. Ren, H.-L. Li, L.-L. Guo, X.-X. Zhang and C. Liao, *Eur. J. Med. Chem.*, 2015, **103**, 185–190; (*b*) S.-S. Xie, J.-S. Lan, X. Wang, Z.-M. Wang, N. Jiang, F. Li and L.-Y. Kong, *Bioorg. Med. Chem.*, 2016, **24**, 1528–1539; (*c*) J. Joubert, G. B. Foka, B. P. Repsold, D. W. Oliver, E. Kapp and S. F. Malan, *Eur. J. Med. Chem.*, 2017, **125**, 853–864; (*d*) A. Stefanachi, F. Leonetti, L. Pisani, M. Catto and A. Carotti, *Molecules*, 2018, **23**, 250–273; (*e*) A. Ibrar, S. A. Shehzadi, F. Saeed and I. Khan, *Bioorg. Med. Chem.*, 2018, **26**, 3731–3762.

28 For reviews, see:(*a*) A. Thakur, R. Singla and V. Jaitak, *Eur. J. Med. Chem.*, 2015, **101**, 476–495; (*b*) J. Dandriyal, R. Singla, M. Kumar and V. Jaitak, *Eur. J. Med. Chem.*, 2016, **119**, 141–168; (*c*) L. F. Zhang and Z. Xu, *Eur. J. Med. Chem.*, 2019, **181**, 111587.

29 K. Pérez-Cruz, M. Moncada-Basualto, J. Morales-Valenzuela, G. Barriga-González, P. Navarrete-Encina, L. Núñez-Vergara, J. A. Squella and C. Olea-Azar, *Arabian J. Chem.*, 2018, **11**, 525–537.

30 (*a*) K. M. Mahadevan, H. N. Harishkumar, J. N. Masagalli and H. T. Srinivasa, *Mol. Cryst. Liq. Cryst.*, 2013, **570**, 20–35; (*b*) V. Y. Korotaev, A. Y. Barkov and V. Y. Sosnovskikh, *Tetrahedron*, 2013, **69**, 9642–9647; (*c*) Y. H. Bai, J. Y. Du and X. X. Weng, *Spectrochim. Acta, Part A*, 2014, **126**, 14–20; (*d*) D. D. Fang, X. Q. Zheng, H. Yi, H. Dai, Z. S. Hong, Y. R. Peng and Y. Y. Lin, *Sens. Actuators, B*, 2019, **283**, 407–414.

31 (*a*) C. L. Xu, G. Y. Yang, C. X. Wang, S. F. Fan, L. X. Xie and Y. Gao, *Molecules*, 2013, **18**, 11964–11977; (*b*) G. Y. Yang, J. T. Yang, C. X. Wang, S. F. Fan, P. H. Xie and C. L. Xu, *J. Fluorine Chem.*, 2014, **168**, 1–8; (*c*) G. Y. Yang, C. X. Wang, S. F. Fan, P. H. Xie, Q. Jin and C. L. Xu, *Chin. J. Org. Chem.*, 2015, **35**, 1173–1178.

32 J.-P. Bao, C.-L. Xu, G.-Y. Yang, C.-X. Wang, X. Zheng and X.-X. Yuan, *Molecules*, 2019, **24**, 1745–1758.

33 (*a*) Y. Z. Xia, Y. Liang, Y. Y. Chen, M. Wang, L. Jiao, F. Huang, S. Liu, Y. H. Li and Z.-X. Yu, *J. Am. Chem. Soc.*, 2007, **129**, 3470–3471; (*b*) F.-Q. Shi, X. Li, Y. Z. Xia, L. M. Zhang and Z.-X. Yu, *J. Am. Chem. Soc.*, 2007, **129**, 15503–15512; (*c*) Y. Liang, S. Liu and Z.-X. Yu, *Synlett*, 2009, 905–909.