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An Efficient Tetrabutylammonium Fluoride (TBAF)-Catalyzed Three-Component Synthesis of 3-Substituted Indole Derivatives under Solvent-Free Conditions

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Abstract: An expedient and efficient one-pot three-component synthesis of 3-substituted indoles has been developed by the reaction of indoles, active methylene compounds and aldehydes using a catalytic amount of tetrabutylammonium fluoride under solvent-free conditions.

Keywords: green chemistry; multicomponent reactions; nitrogen heterocycles; synthetic methods

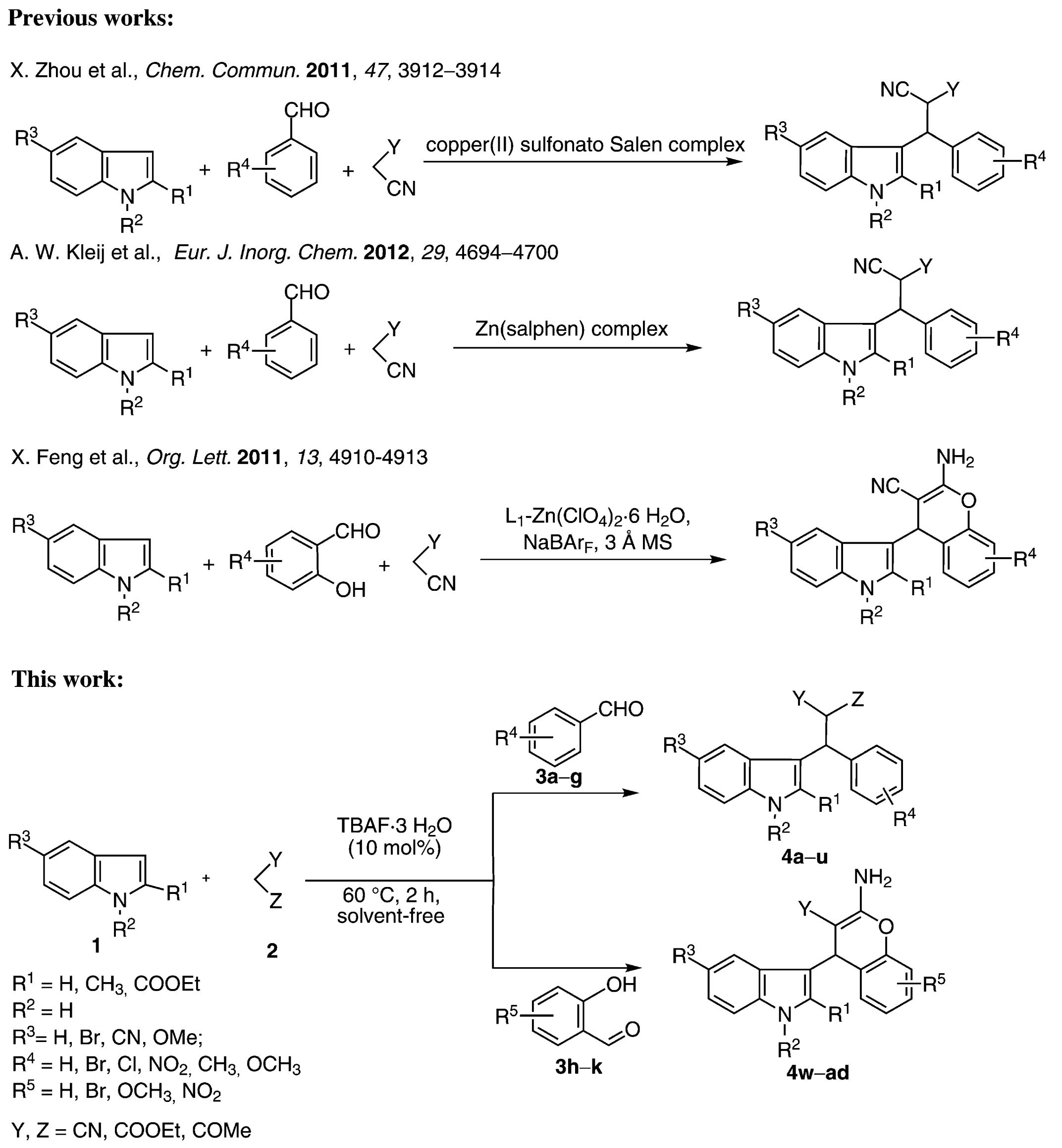
Introduction

One of the current challenges in organic synthesis is the creation of molecular diversity and complexity leading to the preparation of chemo types of biologically active molecules from simple and readily available substrates.[1] Multicomponent reactions (MCRs)[2] offer such convergent chemical processes especially suitable for providing large libraries of bioactive and densely functionalized molecules.[3–5] MCRs are endowed with high levels of atom economy, selectivity, ease of operation and the possibility of automatization.[6]

The indole core nucleus is one of the most intensively studied structural motifs,[7] and a crucial building block for the synthesis of biologically active compounds and natural products.[8,9] Among the different structural patterns, 3-substituted indoles are of special interest as key synthons in planning the synthesis of therapeutic agents and exhibit diverse pharmaceutical activities.[10] For that reason, the synthesis and functionalization of indoles at the C-3 position have been the focal point of active research.[11] Different approaches have been adopted for the synthesis of substituted indoles.[12] However to the best of our knowledge, there exist only two reports on the multicomponent synthesis of 3-substituted indole derivatives utilizing a copper(II) sulfonato Salen complex[13] and a Zn(salphen) complex.[14] As these reports necessitate an additional step to prepare specific Cu and Zn complexes to be used as catalysts and require long reaction times, the processes are cumbersome and expensive. It was therefore deemed worthwhile and important to explore the direct use of an inexpensive and readily available organic species as catalysts for the above reaction.

Chromenes are privileged pharmacological scaffolds frequently found in a number of natural products and biologically active molecules.[15] The current interest in 2-amino-4*H*-chromene derivatives has cropped up due to their potential applications as anticancer, diuretic, spasmolytic, anti-coagulant, anti-anaphylactic, mutagenicial, sex pheromone, anti-tumor, rheumatoid and many other drugs.[16]

Green protocols under solvent-free conditions have presently come to the forefront of current research due to their environmental friendliness and waste reduction.[17] Quaternary ammonium fluorides have been widely recognised as a convenient source of naked fluoride ion which serves as a potential base. Most ionic fluorides are easy to prepare and use and are stable over long periods of time. They react under essentially neutral conditions and are therefore often associated with clean reactions where side reactions are kept to a minimum.[18a] Tetrabutylammonium fluoride (TBAF), in particular, is a cheap, non-toxic, air-stable and eco-safe organocatalyst, and has been extensively used for a variety of base-catalyzed reactions such as the Michael addition, aldol condensation, alkylation, and elimination.[18b–i] The utility of



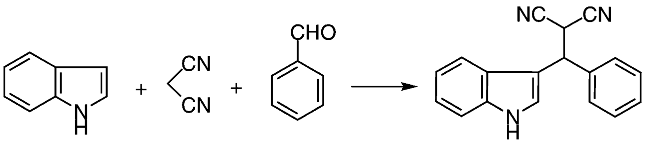
Scheme 1. Comparative illustration of previous and present work.

TBAF in modern organic synthesis has been exploited taking advantage of the eminent basicity of fluoride ion for the direct generation of nucleophiles through a deprotonation process under mild conditions. There is considerable spectroscopic and non-spectroscopic evidence to suggest that the fluoride ion is capable of forming strong H bonds which will result in the transfer of electron density from the anion to the organic substrate, thus enhancing the nucleophilicity of the organic compound while reducing the nucleophilicity of the fluoride.[18j] Kinetic studies on fluoride-promoted reactions have also confirmed the occurrence of H-bonded intermediates.[18k] With all these facts in mind, and as a part of our ongoing research,[19] we have explored the catalytic potential of TBAF·3H$_2$O for a simple and high yielding one-pot green synthesis of 3-substituted indole derivatives under solvent-free conditions (Scheme 1).

Results and Discussion

In order to optimize the reaction conditions, a model reaction using indole (**1a**), malononitrile (**2a**), and benzaldehyde (**3a**), was carried out by varying different parameters and the outcome is given in Table 1. The control experiment in the absence of catalyst and solvent afforded only a low conversion (Table 1, entry 1). A wide range of promoters was then screened. Out of various trials, $FeCl_3$, Fe_3O_4, $ZnCl_2$, CdI_2, PTSA, and P_2O_5 furnished relatively low product yields (entries 2–7), while CAN, and I_2 proved ineffective (entries 8 and 9). Subsequently, we turned

Table 1. Evaluation of reaction conditions for the model reaction.[a]



Entry	Catalyst (mol%)	Solvent	Time [h]	Yield [%][b]
1	–	–	10	10
2	$FeCl_3$ (5)	–	10	15
3	Fe_3O_4 (5)	–	10	20
4	$ZnCl_2$ (5)	–	10	30
5	CdI_2 (5)	–	10	20
6	PTSA (5)	–	10	10
7	P_2O_5 (5)	–	10	10
8	CAN (5)	–	10	nr[c]
9	I_2 (5)	–	10	nr[c]
10	KOH (5)	–	10	65
11	DBU (5)	–	10	67
12	TEA (5)	–	10	55
13	$[Bmim]BF_4$ (5)	–	10	15
14	TBAB (5)	–	10	40
15	TEBA (5)	–	10	20
16	KF (15)	–	10	35
17	TBAF (5)	–	10	73
18	TBAF (10)	–	02	85
19	TBAF (15)	–	02	85
20	TBAF (10)	H_2O	05	80
21	TBAF (10)	CH_3CN	05	65
22	TBAF (10)	$C_6H_5CH_3$	05	32

[a] Using an equimolar (1 mmol) ratio of **1a**, **2a** and **3a** at 60 °C.

[b] Isolated yield after column chromatography.

[c] No reaction.

our attention towards bases like KOH, DBU and triethylamine (TEA), which promoted the reaction to a good extent under solvent-free conditions (entries 10–12). The performance of an ionic liquid $[Bmim]BF_4$ for this purpose was also inadequate (entry 13). Amazingly, when TBAF was used as catalyst under the same set of reaction conditions, we were delighted to observe a remarkably high product yield (entry 18). Intrigued by this study, we were tempted to use some other phase-transfer catalysts and fluoride salts, *viz.*, TBAB, TEBA, and KF, but the catalytic performance of all these was not satisfactory (entries 14–16). Thus, TBAF was opted as the best choice for further studies due to its optimum catalytic efficiency and green credentials. Besides other advantages, the uniqueness of TBAF also stems from its electrophilic bulky quaternary ammonium cation that acts as a Lewis acid for activating carbonyl groups *via* oxygen coordination.

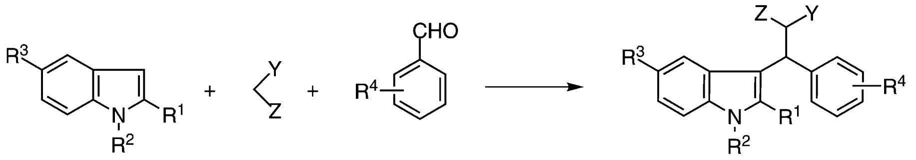
To ascertain the optimum molar catalyst loading of TBAF, the model reaction was carried out using 5, 10 and 15 mol% of TBAF under solvent-free conditions at 60 °C affording 73, 85 and 85% product yields, respectively. Increasing the amount of catalyst (15 mol%) had no added effect on the reaction progress, albeit the reaction remained incomplete when 5 mol% of the catalyst was used. To advance the process further, the optimized catalytic reaction was also probed in different solvents such as water, acetonitrile and toluene at 60 °C (entries 20–22). The best conversion was finally achieved using TBAF (10 mol%) under solvent-free conditions at 60 °C (entry 18).

With the optimum conditions in hand (entry 18), the scope of this methodology was extended to the reaction of a wide range of aromatic aldehydes **3a–g**, different indoles, *viz.*, indole (**1a**), 2-methylindole (**1b**), 5-bromoindole (**1c**), 5-methoxyindole (**1d**), 5-cyanoindole (**1e**), ethyl indole-2-carboxylate (**1f**), and active methylene compounds such as malononitrile (**2a**), ethyl cyanoacetate (**2b**), diethyl malonate (**2c**) and acetylacetone (**2d**).

The findings (Table 2) reveal that all the reactions proceeded smoothly to deliver the products **4a–u** with various structural features in excellent yields. Indoles bearing a cyano group (entries 19–21) and active methylene compounds **2c** and **2d** (entries 16 and 17) gave relatively low product yields, whereas ethyl indole-2-carboxylate (**1f**) was unreactive (entry 22).

The aromatic aldehydes substituted with halogens and electron-withdrawing groups (entries 2–4, 6, 8 and 11) reacted faster and gave higher product yields than those with electron-donating groups (entries 5, 9, 10 and 14). A mixture of 2-methylindole/indole/5-cyanoindole with benzaldehyde and ethyl cyanoacetate under the identical conditions, however, provided the products **4l**, **4m** and **4u** as an inseparable diastereomeric mixture (entries 12, 13 and 21).[20] It is interesting to mention that the reaction with salicylaldehyde did not provide the expected product, rather we were confronted with the formation of 2-amino-4-(indol-3-yl)-4*H*-chromenes *via* a Knoevenagel/Pinner reaction proceeding in accordance with the earlier reports using an *N,N'*-dioxide-Zn(II) complex and $InCl_3$.[21] To extend the scope of this observation, a number of salicylaldehydes (**3h–3k**) and indoles were allowed to react with malononitrile or ethyl cyanoacetate, and the findings are included in Table 3. Salicylaldehydes carrying electron-donating or electron-withdrawing substituents participated well to give the corresponding products. The product structures of ethyl 2-cyano-3-(2-methyl-1*H*-indol-3-yl)-3-phenylpropanoate **(4l)** and ethyl 2-amino-4-(2-methyl-1*H*-indol-3-yl)-4*H*-chromene-3-carboxylate **(4ac)** were conclusively confirmed by their single crystal X-ray determinations (Figure 1 and Figure 2).[22] Based upon the existing literature[18] and isolation of products, a plausible mechanism is outlined in Figure 3. The catalytic efficiency of TBAF in this transformation may be ascribed to the presence of the naked fluoride ion which serves

Table 2. TBAF-catalyzed three-component reaction of indoles, active methylene compounds and aldehydes.[a]



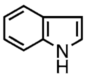
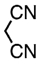
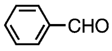
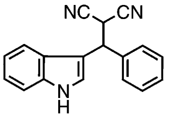
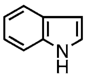
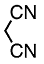
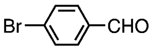
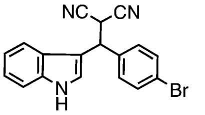
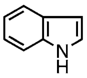
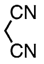
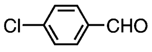
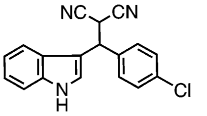
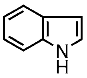
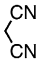
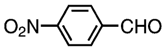
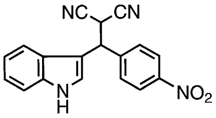
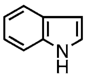
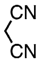
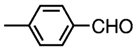
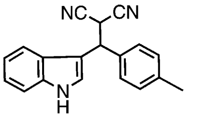
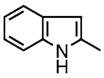
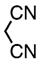
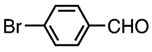
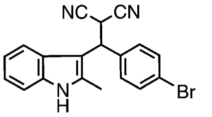
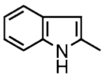
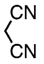
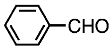
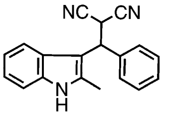
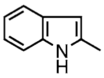
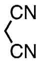
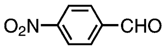
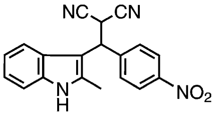
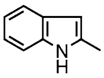
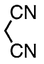
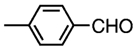
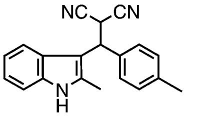
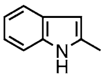
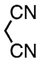
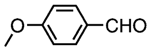
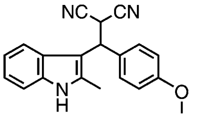
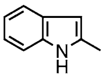
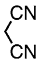
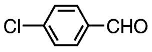
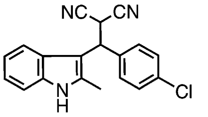
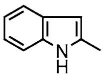
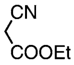
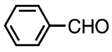
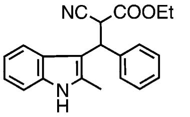
Entry	1		2		3		Product (4)		Yield [%][b]
1		**1a**		**2a**		**3a**		**4a**	85
2		**1a**		**2a**		**3b**		**4b**	90
3		**1a**		**2a**		**3c**		**4c**	90
4		**1a**		**2a**		**3d**		**4d**	95
5		**1a**		**2a**		**3e**		**4e**	78
6		**1b**		**2a**		**3b**		**4f**	91
7		**1b**		**2a**		**3a**		**4g**	86
8		**1b**		**2a**		**3d**		**4h**	97
9		**1b**		**2a**		**3e**		**4i**	80
10		**1b**		**2a**		**3f**		**4j**	82
11		**1b**		**2a**		**3c**		**4k**	92
12		**1b**		**2b**		**3a**		**4l**	93

Table 2. (Continued)

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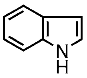
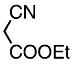
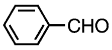
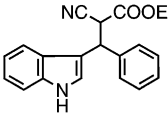
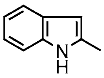
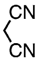
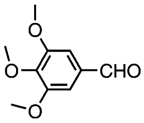
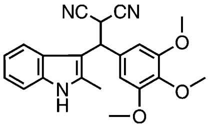
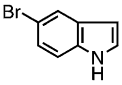
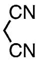
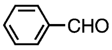
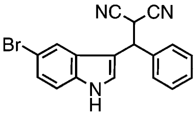
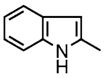
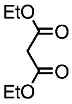
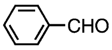
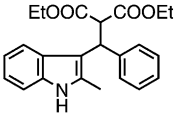
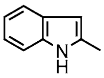
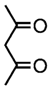
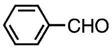
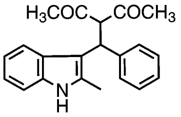
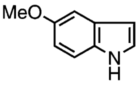
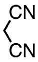
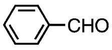
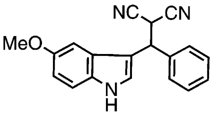
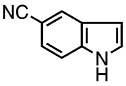
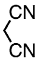
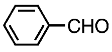
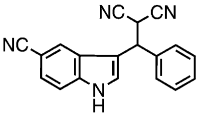
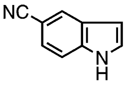
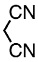
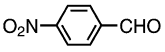
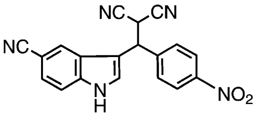
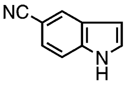
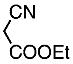
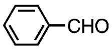
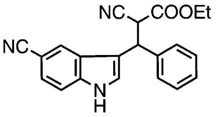
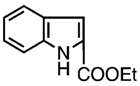
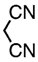
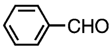
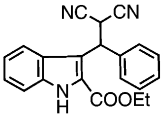
13		**1a**		**2b**		**3a**		**4m**	95
14		**1b**		**2a**		**3g**		**4n**	79
15		**1c**		**2a**		**3a**		**4o**	90
16		**1b**		**2c**		**3a**		**4p**	60
17		**1b**		**2d**		**3a**		**4q**	55
18		**1d**		**2a**		**3a**		**4r**	85
19		**1e**		**2a**		**3a**		**4s**	65
20		**1e**		**2a**		**3d**		**4t**	67
21		**1e**		**2b**		**3a**		**4u**	70
22		**1f**		**2a**		**3a**		**4v**	nr[c]

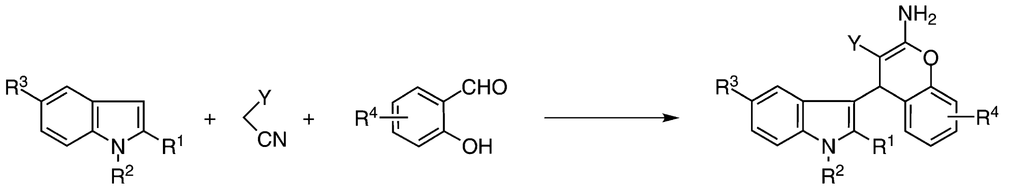
[a] Using an equimolar (1 mmol) ratio of **1**, **2** and **3** at 60 °C.
[b] Isolated yield after column chromatography.
[c] No reaction.

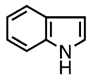
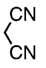
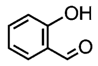
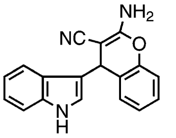
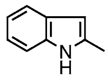
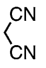
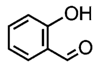
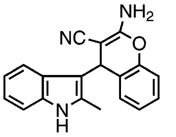
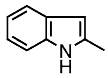
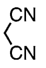
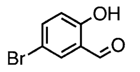
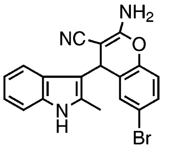
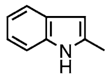
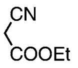
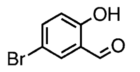
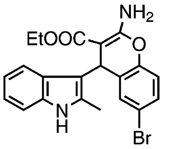
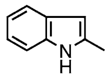
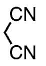
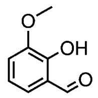
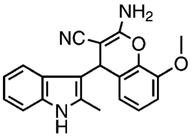
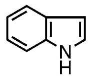
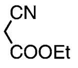
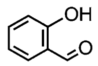
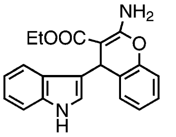
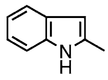
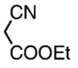
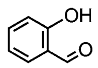
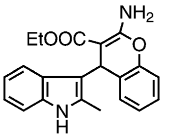
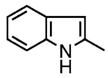
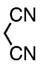
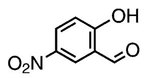
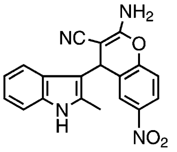
as a base to promote the Knoevenagel condensation between aldehydes and active methylene compounds followed by Michael addition of indole to the resulting arylidene intermediate. The fluoride ion possesses a strong hydrogen bonding capability and the proposed hydrogen bonded intermediates are well described in literature.[18k]

Conclusions

In conclusion, we have developed a green, simple and efficient method for the construction of 3-indole derivatives under solvent-free conditions. Besides the use of an inexpensive, air-stable, mild and environmentally friendly catalyst, the methodology offers a metal-free nature, low catalyst loading, high yield, easy work-up and broad substrate scope.

Table 3. TBAF-catalyzed three component one-pot synthesis of 2-amino-4-(indol-3-yl)-4*H*-chromenes.[a]



Entry	1		2		3		Product (4)		Yield [%][b]
1		**1a**		**2a**		**3h**		**4w**	88
2		**1b**		**2a**		**3h**		**4x**	90
3		**1b**		**2a**		**3i**		**4y**	86
4		**1b**		**2b**		**3i**		**4z**	88
5		**1b**		**2a**		**3j**		**4aa**	90
6		**1a**		**2b**		**3h**		**4ab**	91
7		**1b**		**2b**		**3h**		**4ac**	89
8		**1b**		**2a**		**3k**		**4ad**	92

[a] Using an equimolar (1 mmol) ratio of **1**, **2** and **3** at 60 °C.

[b] Isolated yield after column chromatography.

Experimental Section

General Remarks

All the reactions were carried out in 10-mL borosilicate vials with constant stirring using a Teflon-coated magnetic stir bar under aerobic conditions. Solvents were freshly distilled according to standard procedures. Column chromatography was performed using Merck silica gel (100–200 mesh). Thin layer chromatography (TLC) was performed using Merck GF_{254} plates (thickness 0.25 mm). Visualization of spots on TLC plate was accomplished with UV light and by staining in an I_2 chamber. ^1H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz on a JEOL AL300 F NMR

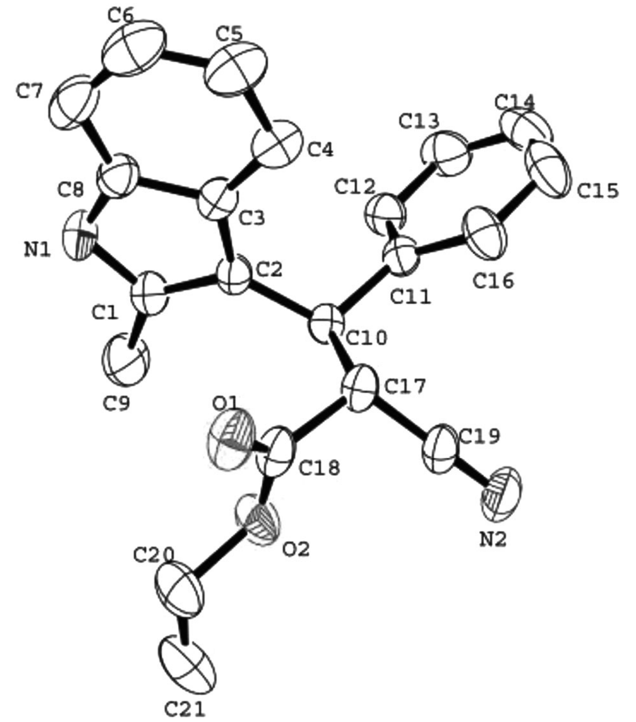


Figure 1. ORTEP diagram of **4l**.

spectrometer. NMR chemical shifts are expressed in δ values with reference to tetramethylsilane (TMS) as internal standard. Product yields refer to isolated yields after column chromatography. Single crystal X-ray data of the products were collected on an Xcalibur Oxford diffractometer.[22]

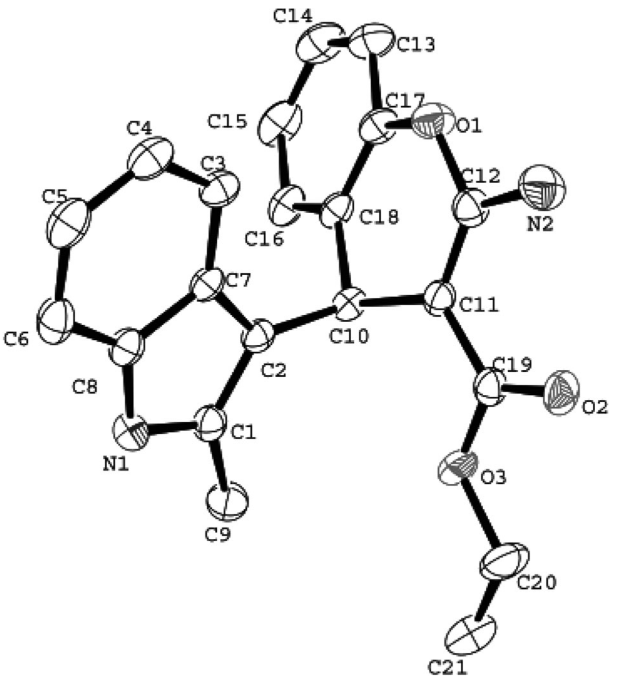


Figure 2. ORTEP diagram of **4ac**.

General Experimental Procedure

A mixture of indole (**1**, 1 mmol), active methylene compound (**2**, 1 mmol), aldehyde/*o*-hydroxy aldehyde (**3**, 1 mmol), and TBAF·3H_2O (0.1 mmol), placed in a 10-mL borosilicate vial, was stirred at 60 °C for the stipulated period of time. In some cases, a small amount of diethyl ether was added for stirring the reaction mixture initially. After completion of the reaction (monitored by TLC), reac-

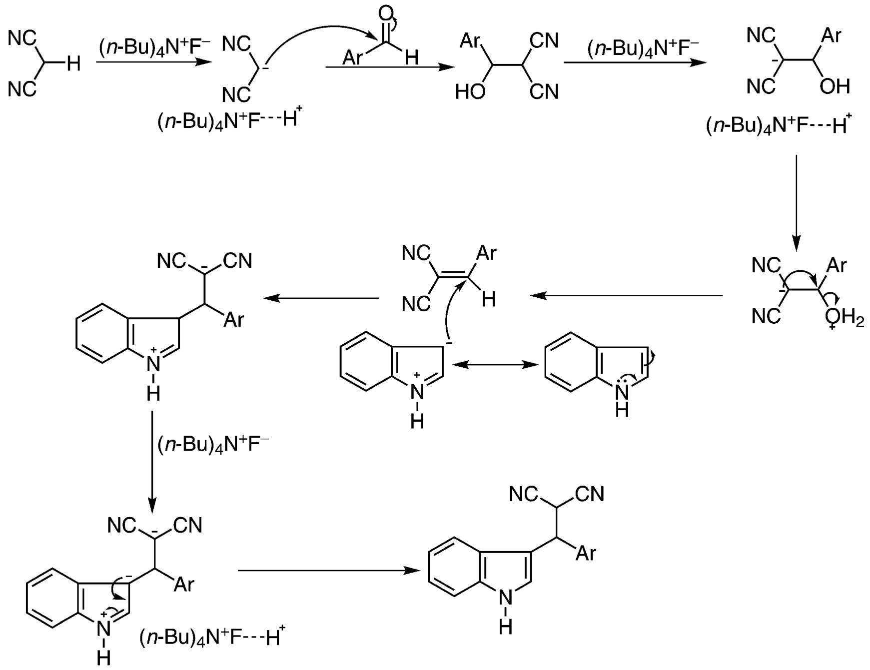


Figure 3. Plausible mechanism for the reaction.

tion mixture was cooled to room temperature. Water was added to it and then extracted with ethyl acetate (3× 10 mL). The organic phase was dried over anhydrous Na_2SO_4, the solvent was evaporated under reduced pressure, and the residue was purified by column chromatography using hexane-ethyl acetate as eluent to afford the pure product.

Acknowledgements

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References

[1] R. V. A. Orru, M. de Greef, *Synthesis* **2003**, 1471–1499.
[2] a) N. Isambert, R. Lavilla, *Chem. Eur. J.* **2008**, *14*, 8444–8454; b) E. Ruijter, R. Scheffelaar, R. V. A. Orru, *Angew. Chem.* **2011**, *123*, 6358–6371; *Angew. Chem. Int. Ed.* **2011**, *50*, 6234–6246.
[3] a) K. C. Nicolaou, R. Hanko, W. Hartwig, in: *Handbook of Combinatorial Chemistry*, Wiley-VCH, Weinheim, **2002**; b) R. E. Dolle, *J. Comb. Chem.* **2003**, *5*, 693–753.
[4] a) S. L. Schreiber, *Science* **2000**, *287*, 1964–1969; b) L. A. Wessjohann, E. Ruijter, *Mol. Diversity* **2005**, *9*, 159–169; c) D. R. Spring, *Org. Biomol. Chem.* **2003**, *1*, 3867–3870; d) M. D. Burke, S. L. Schreiber, *Angew. Chem.* **2004**, *116*, 48–60; *Angew. Chem. Int. Ed.* **2004**, *43*, 46–58; e) R. J. Spandl, A. Bender, D. R. Spring, *Org. Biomol. Chem.* **2008**, *6*, 1149–1158.
[5] a) M. Colombo, I. Peretto, *Drug Discovery Today* **2008**, *13*, 677–684; b) C. Hulme, V. Gore, *Curr. Med. Chem.* **2003**, *10*, 51–80.
[6] C. de Graaff, E. Ruijter, R. V. A. Orru, *Chem. Soc. Rev.* **2012**, *41*, 3969–4009.
[7] a) G. Schneider, U. Fechner, *Nat. Rev. Drug Discovery* **2005**, *4*, 649–663; b) P. S. Baran, C. A. Guerrero, N. B. Ambhaikar, B. D. Hafensteiner, *Angew. Chem.* **2005**, *117*, 612–615; *Angew. Chem. Int. Ed.* **2005**, *44*, 606–609; c) S. B. Herzon, A. G. Myers, *J. Am. Chem. Soc.* **2005**, *127*, 5342–5344; d) M. Bian, Z. Wang, X. Xiong, Y. Sun, C. Matera, K. C. Nicolaou, A. Li, *J. Am. Chem. Soc.* **2012**, *134*, 8078–8081.
[8] T. Eicher, S. Hauptmann, A. Speicher, *The Chemistry of Heterocycles*, Wiley-VCH, Weinheim, **2003**.
[9] J. A. Joule, K. Mills, *Heterocyclic Chemistry*, Blackwell Science Oxford, **2000**.
[10] a) P. Rani, V. K. Srivastava, A. Kumar, *Eur. J. Med. Chem.* **2004**, *39*, 449–452; b) G. W. Gribble, in: *Comprehensive Heterocyclic Chemistry*, 2nd edn., Pergamon Press, New York, **1996**, Vol. 2, Chapter 2.04; c) A. Andreani, S. Burnelli, M. Granaiola, A. Leoni, A. Locatelli, R. Morigi, M. Rambaldi, L. Varoli, L. Landi, C. Prata, M. V. Berridge, C. Grasso, H.-H. Fiebig, G. Kelter, A. M. Burger, M. W. Kunkel, *J. Med. Chem.* **2008**, *51*, 4563–4570; d) M. Lounasmaa, A. Tolvanen, *Nat. Prod. Rep.* **2000**, *17*, 175–191; e) S. Hibino, T. Choshi, *Nat. Prod. Rep.* **2001**, *18*, 66–71; f) D. J. Faulkner, *Nat. Prod. Rep.* **2002**, *19*, 1–49.
[11] a) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, *105*, 2873–2920; b) G. Bartoli, G. Bencivenni, R. Dalpozzo, *Chem. Soc. Rev.* **2010**, *39*, 4449–4465.
[12] a) A. Palmieri, M. Petrini, R. R. Shaikh, *Org. Biomol. Chem.* **2010**, *8*, 1259–1270; b) P. Galzerano, F. Pesciaioli, A. Mazzanti, G. Bartoli, P. Melchiorre, *Angew. Chem.* **2009**, *121*, 8032–8034; *Angew. Chem. Int. Ed.* **2009**, *48*, 7892–7894; c) S.-L. Zhu, S.-J. Ji, K. Zhao, Y. Liu, *Tetrahedron Lett.* **2008**, *49*, 2578–2582.
[13] Y. Qu, F. Ke, L. Zhou, Z. Li, H. Xiang, D. Wu, X. Zhou, *Chem. Commun.* **2011**, *47*, 3912–3914.
[14] D. Anselmo, E. C. Escudero-Adán, M. M. Belmonte, A. W. Kleij, *Eur. J. Inorg. Chem.* **2012**, *29*, 4694–4700.
[15] a) G. P. Ellis, I. M. Lockhart, in: *The Chemistry of Heterocyclic Compounds: Chromenes, Chromanones, and Chromones*, (Ed.: G. P. Ellis), Wiley-VCH, New York, **2007**, Vol. 31, pp 1–1196; b) J. D. Hepworth, C. D. Gabbutt, B. M. Heron, in: *Comprehensive Heterocyclic Chemistry II: Pyrans and their Benzo Derivatives: Synthesis*, (Eds.: A. R. Katritzky, C. W. Rees, E. F. V. Schriven), Pergamon Press, Oxford, **1996**, Vol. 5, pp 351–468; c) D. Kumar, V. B. Reddy, S. Sharad, U. Dube, S. Kapur, *Eur. J. Med. Chem.* **2009**, *44*, 3805–3809; d) W. Kemnitzer, J. Drewe, S. Jiang, H. Zhang, C. Crogan-Grundy, D. Labreque, M. Bubenick, G. Attardo, R. Denis, S. Lamothe, H. Gourdeau, B. Tseng, S. Kasibhatla, S. X. Cai, *J. Med. Chem.* **2008**, *51*, 417–423.
[16] a) W. O. Foye, T. L. Lemke, D. A. Williams, in: *Principi di Chimica Farmaceutica*, Piccin-Nuova Libraria, Padua, Italy, **1991**, pp 416–420; b) L. L. Andreani, E. Lapi, *Bull. Chim. Farm.* **1960**, *99*, 583–586; c) L. Bonsignore, G. Loy, D. Secci, A. Calignano, *Eur. J. Med. Chem.* **1993**, *28*, 517–520; d) G. Shanthi, P. T. Perumal, U. Rao, P. K. Sehgal, *Ind. J. Chem. Sect. B: Org. Chem. Incl. Med. Chem.* **2009**, *48*, 1319–1323.
[17] M. A. P. Martins, C. P. Frizzo, D. N. Moreira, L. Buriol, P. Machado, *Chem. Rev.* **2009**, *109*, 4140–4182.
[18] a) T. Ooi, K. Maruoka, *Acc. Chem. Res.* **2004**, *37*, 526–533; b) J.-L. Zhang, Y.-F. Gong, *Org. Lett.* **2011**, *13*, 176–179; c) J. Hu, L. Liu, S. Yang, Y.-M. Liang, *Org. Biomol. Chem.* **2011**, *9*, 3375–3379; d) J. Hu, L.-Y. Wu, X.-C. Wang, Y.-Y. Hu, Y.-N. Niu, X.-Y. Liu, S. Yang, Y.-M. Liang, *Adv. Synth. Catal.* **2010**, *352*, 351–356; e) X. Q. Wang, P. J. Jia, S. P. Liu, W. Yu, *Chin. Chem. Lett.* **2011**, *22*, 931–934; f) V. Bhalla, A. Gupta, H. Singh, Roopa, M. Kumar, *J. Org. Chem.* **2011**, *76*, 1578–1583; g) D. Amantini, R. Beleggia, F. Fringuelli, F. Pizzo, L. Vaccaro, *J. Org. Chem.* **2004**, *69*, 2896–2898; h) V. Bhalla, H. Singh, M. Kumar, *Org. Lett.* **2010**, *12*, 628–631; i) S. Gao, C. Tseng, C. H. Tsai, C.-F. Yao, *Tetrahedron* **2008**, *64*, 1955–1961; j) J. H. Clark, *Chem. Rev.* **1980**, *80*, 429–452; k) L. Rand, D. Haidukewych, R. J. Dolinski, *J. Org. Chem.* **1966**, *31*, 1272–1274.
[19] a) D. S. Raghuvanshi, A. K. Gupta, K. N. Singh, *Org. Lett.* **2012**, *14*, 4326–4329; b) R. Vanjari, B. K. Allam, K. N. Singh, *RSC Adv.* **2013**, *3*, 1691–1694.
[20] X.-L. Liu, D. Xue, Z.-T. Zhang, *J. Heterocycl. Chem.* **2011**, *48*, 489–494.

[21] a) W. Chen, Y. Cai, X. Fu, X. Liu, L. Lin, X. Feng, *Org. Lett.* **2011**, *13*, 4910–4913; b) G. Shanthi, P. T. Perumal, *Tetrahedron Lett.* **2007**, *48*, 6785–6789.

[22] CCDC 892775 and CCDC 900111 contain the supplementary crystallographic data of the products **4l** and **4ac**, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.