Superacid-Promoted Dual C–C Bond Formation by Friedel–Crafts Alkylation and Acylation of Ethyl Cinnamates: Synthesis of Indanones

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Received: 01.02.2013; Accepted after revision: 17.02.2013

Dedicated to the memory of my mentor Prof. A. Srikrishna (1955–2013), an outstanding organic chemist and a constant source of inspiration.

Abstract: A superacid (triflic acid) promoted dual C–C bond formation via intermolecular Friedel–Crafts alkylation (Michael addition type) and intramolecular acylation for the efficient synthesis of 3-substituted indan-1-ones is presented. This method was successful in activating ethyl cinnamates towards dual aromatic electrophilic substitution. Moreover, it enabled us to synthesize novel spirotetracyclic systems.

Key words: cinnamates, indanones, Friedel–Crafts alkylation, acylation, superacid

One-pot synthetic methods are considered to be the most useful procedures in organic synthesis since they allow constructing more than one bond in a single operation without the need to isolate intermediates. Therefore, the development of such one-pot processes which involves formation of multiple C–C bonds, particularly to construct cyclic structures, are of great interest because many cyclic structures are identified as core structures of many biologically active natural products. In this context, the Friedel–Crafts reaction is considered as one of the most classical and powerful methods for forming C–C bond through alkylation and acylation reactions invented by Friedel and Crafts in 1877.[1] Notably, in the last few decades this reaction has been enormously exploited using various acids (Brønsted and Lewis).[2–4] Significantly, the synthesis of cyclic systems via single or multiple C–C bond formation illustrates the power of the Friedel–Crafts reaction.[5] The importance of superelectrophiles came into light by Olah's research work in the seventies[6] and later researchers made use of superelectrophiles and dicationic electrophiles to construct ring systems efficiently,[3b] because they are more reactive. Herein we disclose a simple and a practical method for the synthesis of 3-substituted indan-1-ones based on a hitherto unexplored superacid (triflic acid) mediated dual C–C bond formation via Friedel–Crafts alkylation (Michael addition type) and acylation. There were very few reports where esters were used as acylating agents.[7] Olah et al. reported the use of methyl benzoate as the acylating agent and quite interestingly, when ethyl acetate was used in place of methyl benzoate no acylated product was formed, rather gave the Friedel–Crafts ethylated product (i.e., via the formation of ethyl carbocation electrophile).[8] This anomaly is in good agreement and reminiscent to that of observed deviations from linearity of the Hammet plot, for the hydrolysis of ethyl benzoates bearing π-electron-withdrawing groups (i.e., an ideal example for concave upward deviation, where it involves the $A_{AL}1$ mechanism for the formation of ethyl carbocation).[9] Recently, the research group of Hashmi et al. reported the use of gold Lewis acid catalysts in the Friedel–Crafts reaction.[10] There was a report by Klumpp et al. in 2004, using cinnamic acids as the source of dicationic intermediates, for the construction of 3-substituted indan-1-ones.[5o] Very recently, the same research group reported another clever synthesis of indanones using more reactive amides as acylating agents (i.e., by keeping the amide nitrogen in extended conjugation with the π-electron-withdrawing groups and thus acts as a good leaving group).[5t] Significance of the present method is based on the direct use of cinnamate esters unlike Klumpp's approach,[5o] which was employed on cinnamic acids in the presence of a large excess of strong acid (100 equiv).

The indanone moiety constitutes the core structural unit of a variety of drugs and natural products which exhibit good range of biological activities. Representative examples of such compounds are pauciflorol F,[11] donepezil,[12] indacrinone,[13] and taiwan-iaquinol B[14] (Figure 1).

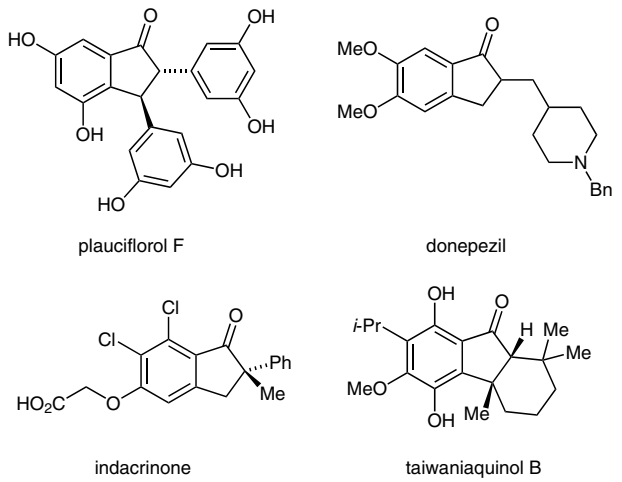
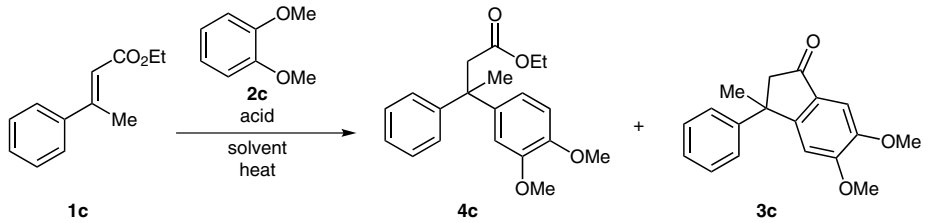


Figure 1 Biologically active indanones

SYNLETT 2013, 24, 0868–0872
Advanced online publication: 06.03.2013
DOI: 10.1055/s-0032-1318405; Art ID: ST-2013-D0109-L

The required cinnamates for this study were prepared from readily available benzaldehydes or corresponding acetophenones using Wittig–Horner–Wadsworth–Emmons reaction. To sort out the best optimized reaction conditions based on the strength of the acid, the cinnamate **1c** (*E*-isomer) was treated with the external arene **2c** under different acidic conditions (Table 1). The initial attempts either with PTSA or with $TiCl_4$ were unsuccessful to yield any product (Table 1, entries 1–3). Whereas, the reaction in the presence of Lewis acid ($FeCl_3$) at ambient temperature gave only the alkylated product **4c**, whose yield increased in parallel to the quantity of the acid used (Table 1, entries 4 and 5). This gave a clear indication that the enoate double bond is more reactive than the carbonyl bond of the ester function and thus preferentially alkylated first. Subsequent increase of temperature as well as the quantity of the Lewis acid started to furnish the cyclized product **3c** with the optimized yield 62% (Table 1, entries 6–10). The reaction in the presence of Brønsted superacid (TfOH, 3 equiv) gave a promising result of **3c** as an exclusive product in very good yield (84%, Table 1 entry 11). On the other hand, the reaction in the presence of gold catalysts proved to be unproductive (Table 1, entries 12 and 13).

Table 1 Optimization Conditions for the Synthesis of 3-Indanones **3c**

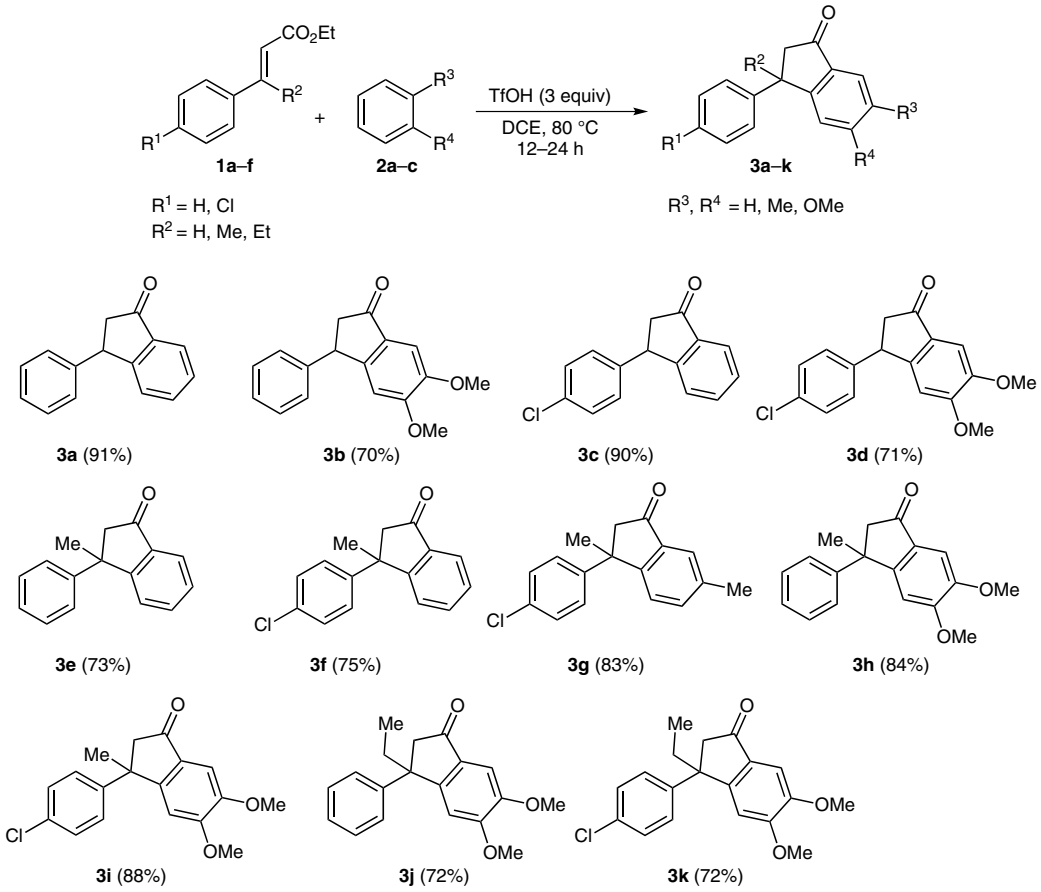


1c **4c** **3c**

Entry[a]	Acid (equiv)	Solvent (mL)	Temp (°C)	Time (h)	Yield of **4c** (%)[b]	Yield of **3c** (%)[b]
1	PTSA (0.2)	toluene (3)	120	24	0[c]	0[c]
2	PTSA (0.3)	DMF (2)	140	24	0[c]	0[c]
3	$TiCl_4$ (0.3)	CH_2Cl_2 (2)	r.t.	96	0[c]	0[c]
4	$FeCl_3$ (0.3)	CH_2Cl_2 (2)	r.t.	12	30	0[e]
5	$FeCl_3$ (0.7)	CH_2Cl_2 (2)	r.t.	12	69	0[e]
6	$FeCl_3$ (0.7)	DCE (2)	80	12	18	43
7	$FeCl_3$ (3)	$CHCl_3$ (2)	60	12	12	54
8	$FeCl_3$ (1.5)	DCE (2)	80	12	0	42
9	$FeCl_3$ (2)	DCE (2)	80	12	0[d]	44
10	$FeCl_3$ (3)	DCE (2)	80	12	0[d]	62
11	TfOH (3)	DCE (2)	80	12	0[d]	84
12	$(PPh_3)_3AuCl$ (0.05)	DCE (2)	80	12	0	0
13	30% $AuCl_3$ in dil. HCl (0.1)	DCE (2)	100	20	9	0

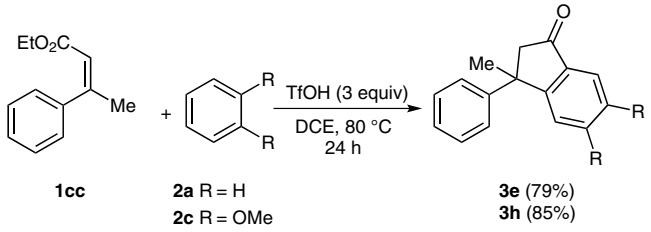
[a] All reactions were carried out on 100 mg (1 equiv) scale of **1c** (*E*-isomer) and 109 mg (1.5 equiv) of **2c**.
[b] Isolated yields of chromatographically pure products.
[c] Neither **4c** nor **3c** were observed, only starting material was recovered.
[d] No **4c** was formed.
[e] No **3c** was identified.

Among the screened conditions, three equivalents of triflic acid (Table 1, entry 11) turned out to be the best with regard to the yield of indanone product **3c**. Therefore, these optimized conditions were applied to the other systems **1a**–**f** (*E*-isomers) to examine the scope and limitations. Interestingly, these optimized reaction conditions proved to be amenable for various systems possessing electron-withdrawing and electron-donating substituents and furnished the cyclized products **3a**–**k**[15] in very good to excellent yields (Scheme 1). It is noteworthy to mention that this had been planned in such a way that the aromatic moiety of all cinnamates **1a**–**f** is more electron deficient than that of the external arenes **2a**–**c** employed. Therefore, only the external arene **2** was involved in the formation of both new C–C bonds with the ethyl cinnamate **1**.



Scheme 1 Superacid-promoted synthesis of indanones **3a**–**k** from cinnamates **1a**–**f** (*E*-isomers)

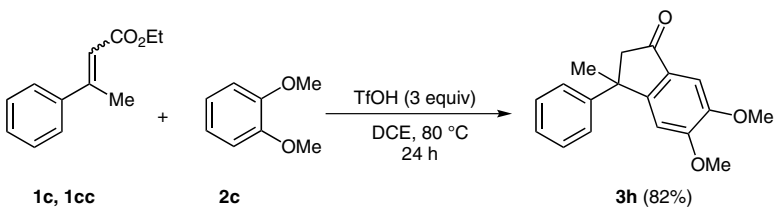
In order to check the feasibility of the reaction, we have explored the reaction on the *Z*-isomer **1cc**. Gratifyingly, the expected indanones **3e** and **3h** resulted in yields comparable to that of the *E*-isomers (Scheme 2).



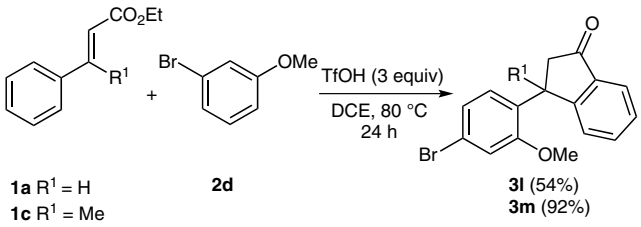
Scheme 2 Superacid-promoted synthesis of 3-indanones **3e** and **3h** from the *Z*-isomer **1cc**

Similar result was obtained, when the reaction was conducted on the mixture of *E*- and *Z*-isomers **1c** and **1cc** (4:1 ratio) with the external arene **2c** (Scheme 3).

Interestingly, when ethyl cinnamates **1a** and **1c** (*E*-isomers) were treated with arene **2d**, in the presence of triflic acid, the simple benzene ring of ethyl cinnamate has been involved in the intramoleclar Friedel–Crafts acylation after the initial Friedel–Crafts alkylation by 3-bromoanisole (**2d**, Scheme 4). This may be due to the weakly deactivating inductive effect of 5-Br and 3-OMe groups to the incoming arylating moiety.

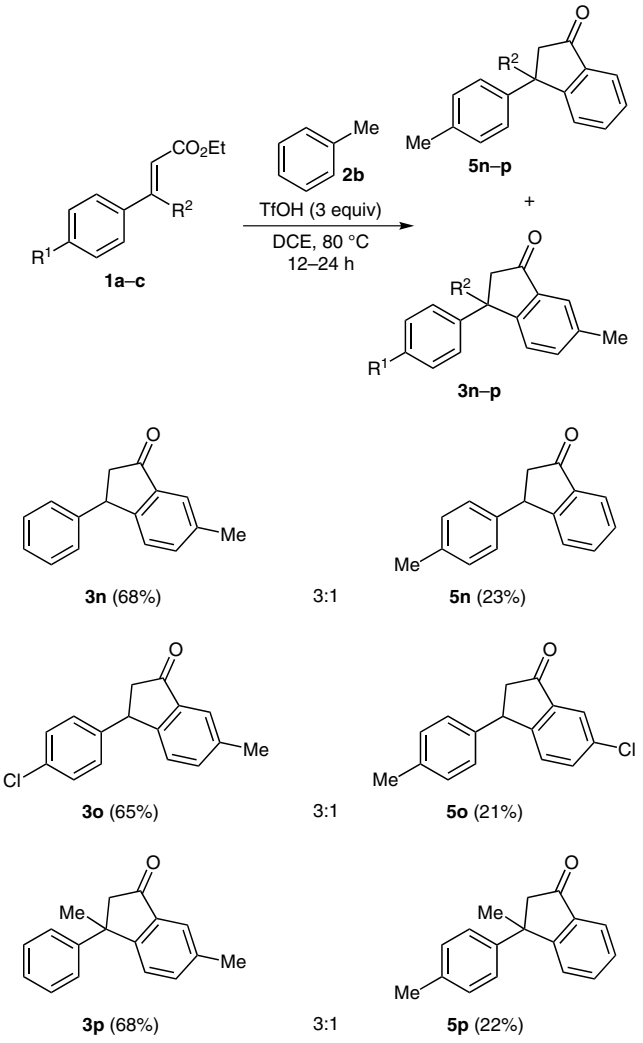


Scheme 3



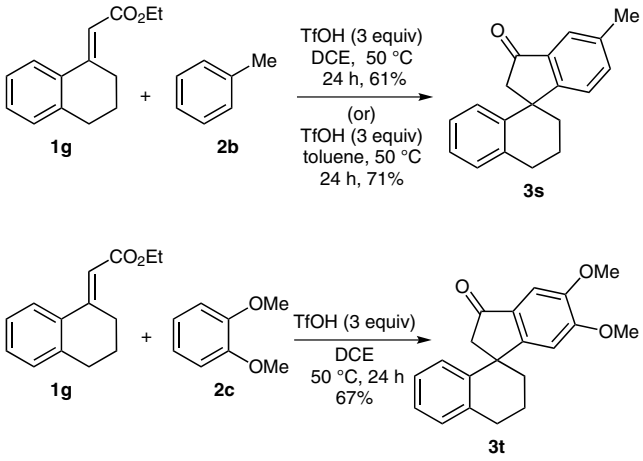
Scheme 4 Superacid-promoted synthesis of 3-indanones **3l** and **3m**

Moreover, we also attempted the reaction where both the aryl moieties can compete with each other in the intramolecular acylation step after initial alkylation. Therefore, two possible products were isolated, as expected, as an inseparable mixture (Scheme 5).



Scheme 5 Superacid-promoted synthesis of indanones **3n**–**p** and **5n**–**p** from cinnamates **1a**–**c** (*E*-isomers)

Furthermore, to check the scope and applicability of the method, we explored the reaction on a cyclic equivalent of cinnamate ester, for the synthesis of novel spirotetracyclic systems. Therefore, the enoate **1g** treated with toluene (**2b**) as well as veratrole (**2c**). Delightfully, the reaction was successful at little lower temperature and furnished the expected novel spirotetracyclic systems **3s** and **3t** (Scheme 6). It has been observed that toluene (**2b**) plays a dual role both as a solvent and external arene (Scheme 6).



Scheme 6

In summary, we have developed a simple and an efficient one-pot dual C–C bond formation via an intermolecular Friedel–Crafts alkylation (Michael addition type) and subsequent intramolecular Friedel–Crafts acylation for the synthesis of functionalized 3-substituted indan-1-ones. This method was successfully applied to the synthesis of novel spirotetracyclic systems. Further studies to make use of this method for the preparation of various cyclic systems are in progress.

Acknowledgment

Financial support by the Council of Scientific and Industrial Research [(CSIR), 02(0018)/11/EMR-II], New Delhi, is gratefully acknowledged. B.V.R and A.G.K. thank CSIR, New Delhi, for the award of research fellowship.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(15) **General Procedure for Friedel–Crafts Alkylation and Acylation of Ethyl Cinnamates (GP-1)**

To an oven-dried Schlenk tube under nitrogen atmosphere were added ester **1** (100 mg, 0.42–0.57 mmol), arene **2** (in case of benzene, toluene, and xylene 12 equiv and for other electron-rich arenes 1.5 equiv were used for 1 equiv of ester **1**) and DCE (2 mL), followed by the addition of TfOH [3 equiv (i.e., 1.26–1.71 mmol)]. The resultant reaction mixture was stirred at 80 °C for 12–24 h. Progress of the reaction was monitored by TLC until the reaction was completed. The reaction mixture was quenched by the addition of aq $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with sat. NaCl solution, dried (Na_2SO_4), and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography (PE–EtOAc) furnished the indanone **3** (54–92%).

Representative Analytical Data

Compound **3f**: IR (MIR-ATR, 4000–600 cm^{-1}): 2966, 2930, 1710, 1602, 1491, 1462, 1288, 1234, 1151, 1093, 1012, 828, 762, 674, 582 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, 1 H, *J* = 7.3 Hz, ArH), 7.60 (dd, 1 H, *J* = 7.8, 7.3 Hz, ArH), 7.43 (dd, 1 H, *J* = 7.8, 7.3 Hz, ArH), 7.25 (d, 1 H, *J* = 7.8 Hz, ArH), 7.24 (ddd, 2 H, *J*=8.8, 2.4, 2.4 Hz, ArH), 7.10 (ddd, 2 H, *J* = 8.8, 2.4, 2.4 Hz, ArH), 2.91 (d, 1 H, *J* = 19.1 Hz, CH_aH_bCO), 2.88 (d, 1 H, *J* = 19.1 Hz, CH_aH_bCO), 1.81 [s, 3 H, $ArC(CH_2CO)CH_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.3 (s, C=O), 162.3 (s, ArC), 145.8 (s, ArC), 135.6 (s, ArC), 135.4 (d, ArCH), 132.3 (s, ArC), 128.5 (d, 2 C, ArCH), 128.0 (d, ArCH), 127.7 (d, 2 C, ArCH), 125.4 (d, ArCH), 123.4 (d, ArCH), 55.5 (t, CH_2CO), 45.6 [s, $ArC(CH_2CO)CH_3$], 28.3 [q, $ArC(CH_2CO)CH_3$] ppm. HRMS (APCI$^+$): *m/z* calcd for $[C_{16}H_{14}ClO]^+$: 257.0728 $[M + H]^+$; found: 257.0724.

Compound **3g**: IR (MIR-ATR, 4000–600 cm^{-1}): 2964, 2851, 1705, 1581, 1488, 1399, 1282, 1244, 1160, 1093, 826, 724, 665, 588 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.57 (s, 1 H, ArH), 7.42 (d, 1 H, *J* = 7.8 Hz, ArH), 7.22 (ddd, 2 H, *J* = 8.8, 2.4, 2.4 Hz, ArH), 7.14 (d, 1 H, *J* = 7.8 Hz, ArH), 7.10 (ddd, 2 H, *J* = 8.8, 2.4, 2.4 Hz, ArH), 2.89 (d, 1 H, *J* = 19.1 Hz, CH_aH_bCO), 2.87 (d, 1 H, *J* = 19.1 Hz, CH_aH_bCO), 2.42 (s, 3 H, $ArCH_3$), 1.78 [s, 3 H, $ArC(CH_2CO)CH_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.4 (s, C=O), 159.7 (s, ArC), 146.1 (s, ArC), 138.0 (s, ArC), 136.6 (d, ArCH), 135.9 (s, ArC), 132.2 (s, ArC), 128.5 (d, 2 C, ArCH), 127.6 (d, 2 C, ArCH), 125.1 (d, ArCH), 123.3 (d, ArCH), 55.8 (t, CH_2CO), 45.3 [s, $ArC(CH_2CO)CH_3$], 28.3 [q, $ArC(CH_2CO)CH_3$], 21.1 (q, $ArCH_3$) ppm. HRMS (APCI$^+$): *m/z* calcd for $[C_{17}H_{16}ClO]^+$: 271.0884 $[M + H]^+$; found: 271.0880.

