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$FeCl_3$-Catalyzed Combinatorial Synthesis of Functionalized Spiro[Indolo-3,10′-indeno [1,2-*b*]quinolin]-trione Derivatives

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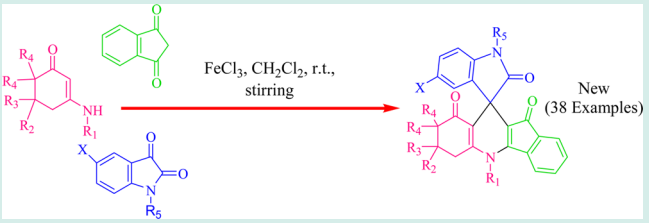
Supporting Information

ABSTRACT: An efficient, inexpensive, environmentally friendly and high yield one-pot route to new spiro[indolo-3,10′-indeno [1,2-*b*]quinolin]-trione derivatives has been developed, involving three-component reaction of enaminones, N-substituted isatins and Indane-1,3-dione catalyzed by $FeCl_3$. The approach to this spiro-heterocycle is noteworthy because it results in the formation of three new σ (two C−C and one C−N) bonds in a single operation, leading to the construction of novel spiro skeleton. This method works on a large scale in excellent yields.



KEYWORDS: *environmentally friendly, multicomponent reactions, isatins, spirocyclic compounds, Lewis acid catalysis, ferric trichloride*

INTRODUCTION

Multicomponent reactions (MCRs) are important tools for medicinal and organic chemists because they offer significant advantages over the stepwise convergent construction of complex molecules.[1] The structurally diverse enaminones have been of longstanding interest for the construction of biologically relevant core structures via multicomponent reactions (MCRs).[2] Examples of such heterocyclic spiro-fragments are shown in Figure 1,[3] including those derived from isatin,[4] quinoline,[5]

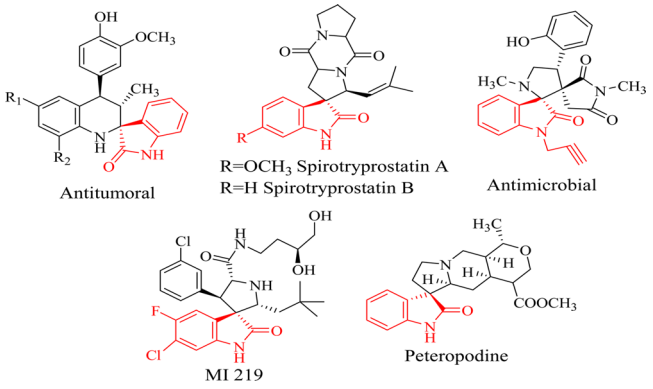
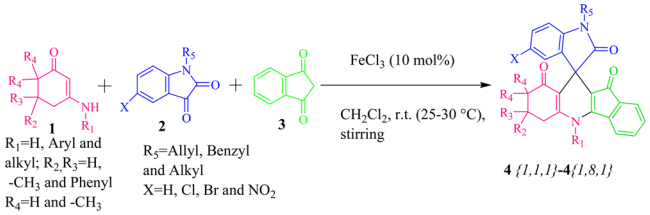


Figure 1. Examples of biologically important fused spiro-compounds.

indenone,[6] and indole,[7] building blocks. Furthermore, C-3 spiroindoline compounds[8] represents an important structural unit found in many natural alkaloids[9] such as spirotryprostatins A and, B, which function as inhibitors of microtubule assembly, and pteropodine and isopteropodine alkaloids, which interact with muscarinic serotonin receptors. In this chemistry, our attention has been drawn to iron(III) chloride as a green and efficient Lewis acid catalyst for C−C bond and carbon−heteroatom formation[10,11] including MCRs under mild reaction conditions.[12] Several $FeCl_3$-based isatin-based multicomponent methods have been reported for the synthesis of spiro-[indolo-3,10′-indeno [1,2-*b*]quinolin]-triones heterocycles[4] and related molecules.[13]

We describe here the extension of $FeCl_3$-catalyzed three-component coupling methodology to commercially available cyclic1,3-dicarbonyl compounds, amines and isatins for the synthesis of highly functionalized spiro-derivatives (Scheme 1). This process provides good to excellent yields of the desired compounds under mild conditions.

Scheme 1. MCR Synthesis of Spiro[Indolo-3,10′-indeno-[1,2-*b*]quinolin]-triones Heterocycles



RESULTS AND DISCUSSION

Reaction Conditions. Enaminone **1**{*1*}, N-substituted isatin **2**{*1*}, and indane 1,3-dione **3**{*1*} served as model substrates to explore the three-component reaction conditions in the presence of various Lewis acidic catalysts in organic solvent (Figure 2, Table 1). $FeCl_3$ (10 mol %) was found to be

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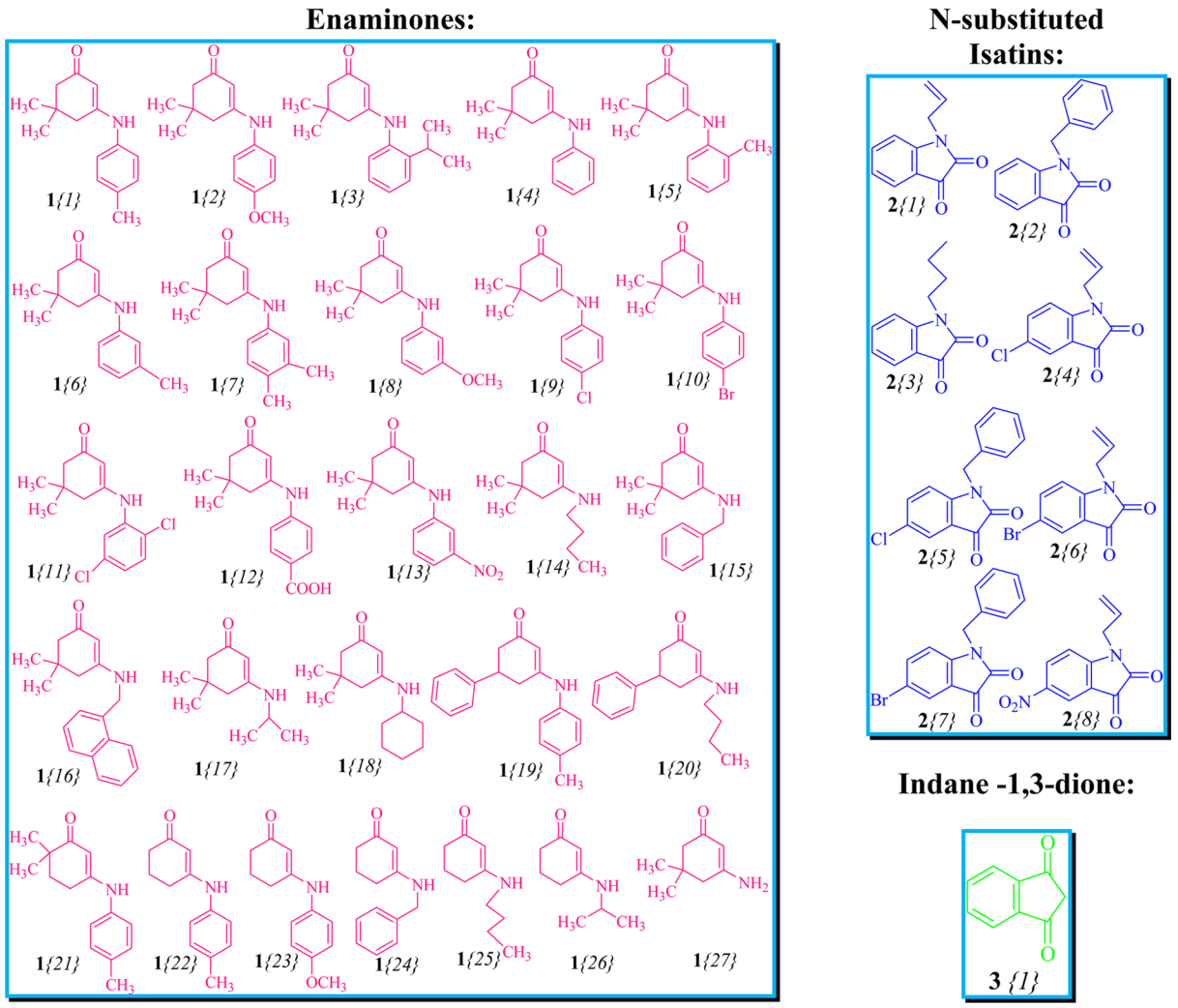

Figure 2. Enaminone and isatin reagents tested in $FeCl_3$-catalyzed multicomponent condensation.

the best catalyst, giving **4**{*1,1,1*} in 92% yield (Table 1, entry 5). While diminishing (entry 6) or increasing (entry 7) the amount of catalyst made no significant difference, the presence of catalyst was required (entry 1). Other Lewis acids (entries 2−4) and mild protic acids (entries 8 and 9) gave the same product in moderate yield, but HCl provided only trace amounts, perhaps because of decomposition of the product in the presence of strong acid. Among the organic solvents tested (CH_3CN, EtOH, MeOH, toluene, THF, DMF and DMSO; entries 11−17), CH_2Cl_2 gave the best yields by substantial amounts.

Substrate Scope. With favorable reaction conditions established (10 mol % $FeCl_3$, CH_2Cl_2 solvent, room temperature), the substrate scope of this $FeCl_3$-catalyzed MCRs process was explored with 27 enaminones (**1**{*1*}−**1**{*27*}), 8 N-substituted isatins (**2**{*1*}−**2**{*8*}) and indane-1,3-dione (**3**{*1*}) (Figure 2 and Table 2).

Various 5,5 disubstituted enaminones **1** were found to give corresponding products **4**{*1,1,1*}−**4**{*18,1,1*}, in yields ranging from 60% to 93% (Table 2, entries 1−11). Unsubstituted enaminones also gave good yields (Table 2, entries 18−20, 24, 25, 27, and 31). Phenyl substitution at the 5 position (**1**{*19*} and **1**{*20*}), as well as 6,6-disubstitution (**1**{*21*}) provided lower yields (Table 2, entries 12, 16, 17, 34), the latter most probably due to steric factors. The electronic nature of N-aryl enaminone substituents had little effect, with electron-donating (methyl, isopropyl, methoxy) or electron-withdrawing (chloro, bromo, nitro, carboxylic acid) aromatic groups (R_1) giving similar results (Table 2, entries 1−6).

N-Alkyl enaminones also gave good yields (Table 2, entries 7−10) with this method. To further broaden the scope of this reaction, we investigated the electronic properties of the substituents (X = chloro, bromo, and nitro) at the isatin C5 position and the N-substituent (R_5 = allyl, benzyl, and *n*-butyl). Each variation was well tolerated, giving structurally diverse spiro-products in excellent yields (82−94%). Note that N-protected isatins bearing electron-withdrawing substituents (X) at the C5 position afforded reproducibly higher yields than other analogues, suggesting an electronic effect (Table 2, entries 23−38).

Enaminones derived from acyclic 1,3-diketones (**5**{*1*−*3*}) also proved to be effective in this ferric-caralyzed process, reacting cleanly with isatins (**3**{*1,2,4*}) and indane-1,3-dione (**3**{*1*}) compounds under the same reaction conditions. The corresponding spiro[indolo-3,4′-indeno[1,2-*b*]pyridin]-2,5′dione derivatives were isolated in good yields (75−85%, Scheme 2, **6**{*1,1,1*}−**6**{*3,4,1*}). All compounds were characterized by ^1H, ^{13}C NMR, and IR spectroscopy analysis.

To the best of our knowledge, this is the first report of the synthesis of spiro-heterocycle using $FeCl_3$ as a lewis acid catalyst via multicomponent protocols and is perfectly amenable to

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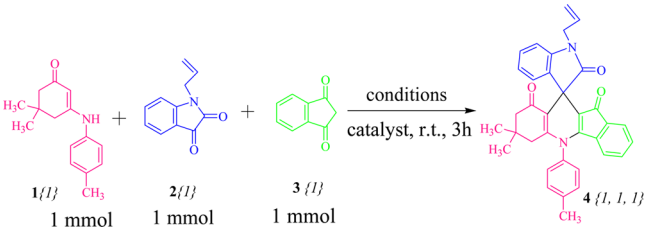
Table 1. Optimization of Reaction Conditions for the Synthesis of Compound 4{*1,1,1*}[a]



entry	catalyst (mol %)/solvent	yield[b] 4{*1,1,1*} (%)
1	none (−), DCM	5
2	$AlCl_3$(10), DCM	45
3	$SnCl_2$ (10), DCM	32
4	$ZnCl_2$ (10), DCM	35
5	**$FeCl_3$ (10), DCM**	**92**
6	$FeCl_3$(5), DCM	80
7	$FeCl_3$(20), DCM	87
8	AcOH (5), DCM	55
9	H_3BO_3 (5), DCM	38
10	HCl (5), DCM	trace
11	$FeCl_3$ (5), ACN	75
12	$FeCl_3$(5), EtOH	65
13	$FeCl_3$(5), MeOH	52
14	$FeCl_3$(5), Tolune	66
15	$FeCl_3$(5), THF	55
16	$FeCl_3$(5), DMF	30
17	$FeCl_3$(5), DMSO	25

[a]Reaction conditions: enaminone (**1**{*1*}, 1 mmol), isatin (**2**{*1*}, 1 mmol), indane-1,3-dione (**3**{*1*}, 1 mmol), different catalysts, different solvents. [b]Yields of isolated products.

automation for combinatorial synthesis. Here, lewis acidic nature of $FeCl_3$ helps to coordinate with oxygen and nitrogen atoms, thereby increasing the electrophilic character of carbonyl carbon and finally, facilitating the dehydration process[6,14] (A detailed mechanistic pathway is proposed in Supporting Information.) The structures of the above spiro-compounds were confirmed unambiguously from single crystal Xray diffraction of the compound **4**{*16,1,1*} and all the compounds were well characterized by ^1H, ^{13}C NMR and IR spectroscopy. The ORTEP plot of compound **4**{*16,1,1*} (Figure 3) is shown in Supporting Information 1.

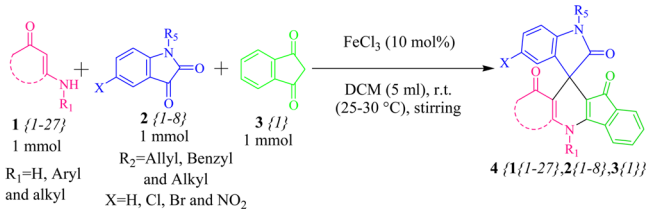
CONCLUSION

In summary, we have successfully developed a novel, straightforward, cheap, and environmentally friendly one-pot three-component reaction to synthesize highly functionalized spiro[indolo-3,10′-indeno [1,2-*b*]quinolin]-2,9′,11′triones derivatives in DCM at room temperature (25−30 °C) in the presence of the Lewis acid catalyst $FeCl_3$ (10 mol %). The procedure has the following advantages: (1) it is highly efficient, has good atom economy and uses an ecologically benign multicomponent reaction strategy, (2) a wide variety of functional groups are tolerated, (3) the $FeCl_3$ catalyst is easily available and environmentally friendly, and (4) it should be readily scalable.

EXPERIMENTAL PROCEDURES

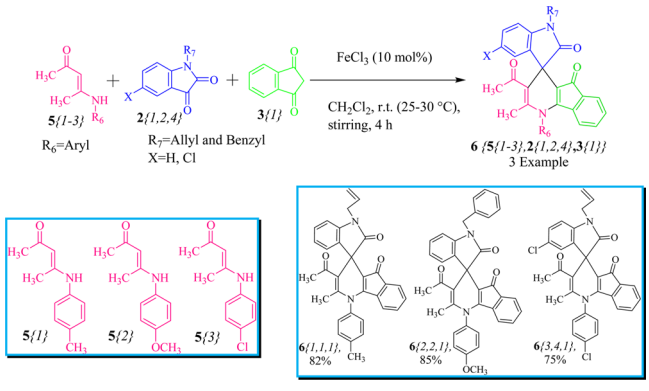
Representative Procedure for $FeCl_3$-Catalyzed Three Component Synthesis of Functionalized Spiro Derivatives. A 25 mL flask was charged with a mixture of enamenones

Table 2. Synthesized Spiro Compounds



entry	product (4)	time (h)	yield (%)	mp (°C)
1	4{*1,1,1*}	3	92	286−288
2	4{*2,1,1*}	3	93	280−282
3	4{*3,1,1*}	4	86	240−242
4	4{*9,1,1*}	3.5	90	304−305
5	4{*12,1,1*}	4	88	132−134
6	4{*13,1,1*}	4	87	310−312
7	4{*14,1,1*}	5	74	158−160
8	4{*15,1,1*}	3.5	83	248−250
9	4{*16,1,1*}	3	85	280−281
10	4{*17,1,1*}	5	75	238−240
11	4{*18,1,1*}	3.5	84	254−255
12	4{*20,1,1*}	6	60	254−256
13	4{*23,1,1*}	3.5	92	340−342
14	4{*6,2,1*}	3.5	85	278−279
15	4{*10,2,1*}	3	86	292−293
16	4{*19,2,1*}	5	72	200−202
17	4{*20,2,1*}	6	65	210−212
18	4{*23,2,1*}	3	87	328−330
19	4{*24,2,1*}	4	70	296−298
20	4{*25,2,1*}	5	75	277−278
21	4{*2,3,1*}	3.5	88	266−268
22	4{*15,3,1*}	3	80	268−270
23	4{*10,4,1*}	3	91	258−260
24	4{*22,4,1*}	3.5	86	>350
25	4{*25,4,1*}	6	72	216−218
26	4{*7,5,1*}	2.5	94	328−330
27	4{*26,5,1*}	4	83	336−338
28	4{*27,5,1*}	3.5	82	>350
29	4{*4,6,1*}	3	92	308−310
30	4{*5,6,1*}	3.5	88	320−322
31	4{*22,6,1*}	3	88	>350
32	4{*8,7,1*}	3	90	>350
33	4{*11,7,1*}	5	84	340−342
34	4{*21,7,1*}	3	75	318−320
35	4{*1,8,1*}	2	92	284−286

Scheme 2. Synthesis of Spiro[Indolo-3,4′-indeno-[1,2-*b*]pyridin]-2,5′diones Derivatives



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(**1**, 1 mmol), N-protected isatin (**2**, 1 mmol), indane-1,3-dione (**3**, 1 mmol), and a catalytic amount of anhydrous $FeCl_3$ (16 mg, 0.1 mmol) in dichloromethane (5 mL). The mixture was magnetically stirred at room temperature (25−30 °C) for the appropriate time mentioned in Table 2. The progress of the reaction was monitored by TLC. After completion of the reaction the mixture was poured into water. Then it was extracted with DCM (20 mL) for three times and followed by brine solution. Next, it was dried over Na_2SO_4, and evaporated under reduced pressure to remove the excess solvent. Finally the crude residue was directly purified by silica gel column chromatography using 30% ethyl acetate in petroleum ether (60−80 °C) as eluant to afford the desired product as red solid. All the obtained products were characterized by ^{1}H NMR, ^{13}C NMR, and IR spectral data. The spectra data for two representative compounds are given as follows.

1-Allyl-7′,7′-dimethyl-5′-p-tolyl-1,3,6′,7′,8′-pentahydro-5H-spiro[indolo-3,10′-indeno [1,2-b]quinolin]-2,9′,11′triones: (Table 2, **4**{*1,1,1*}) yield 92% (484 mg); red solid; mp 286−288 °C (EtOH); R_f [50% EtOAc/petroleum ether (60−80 °C)] 0.60; IR (ν_{max}, KBr, cm^{-1}) 3044, 2955, 2343, 1719, 1690, 1654, 1631, 1487, 1396, 1356, 1281, 1172, 1086, 897, 739, 501; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.30−7.04 (m, 6H, ArH), 6.94 (t, J = 7.4 Hz, 2H, ArH), 6.82−6.72 (m, 3H, ArH), 6.02−5.92 (m, 1H, allyl-CH), 5.58−5.52 (m, 1H, N−CH_2), 5.20 (d, J = 10.5 Hz, 1H, N−CH_2), 5.12 (d, J = 7.5 Hz, 1H, ArH), 4.46−4.41 (m, 2H, allyl-CH_2), 2.42 (s, 3H, Ar−CH_3), 2.18−2.10 (m, 2H, CH_2), 1.97 (d, J = 17.4 Hz, 2H, CH_2), 0.84 (d, J = 18.0 Hz, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 194.9, 190.1, 177.8, 154.5, 152.5, 143.3, 140.7, 136.8, 135.7, 134.6, 133.1, 132.1, 131.3, 130.7, 129.5, 129.0, 128.2, 122.4, 121.9, 121.3, 121.0, 117.2, 114.6, 110.3, 108.7, 50.0, 47.3, 43.1, 41.2, 32.2, 29.4, 26.5, 21.3; Anal. Calcd for $C_{35}H_{30}N_2O_3$ C 79.82, H 5.74, N 5.32; Found C 79.98, H 5.77, N 5.24%.

1-Butyl-5′-(4-methoxy-phenyl)-7′,7′-dimethyl-1,3,6′,7′,8′-pentahydro-5H-spiro[indolo-3,10′-indeno[1,2-b]quinolin]-2,9′,11′triones: (Table 2, **4**{*2,3,1*}) yield 88% (492 mg); red solid; mp 266−268 °C (EtOH); R_f [50% EtOAc/petroleum ether (60−80 °C)] 0.70; IR (ν_{max}, KBr, cm^{-1}) 2956, 2345, 1719, 1661, 1511, 1403, 1360, 1251, 1086, 986, 677; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.44−7.35 (m, 2H, ArH), 7.28−7.20 (m, 2H, ArH), 7.12−7.06 (m, 4H, ArH), 6.95−6.90 (m, 3H, ArH), 5.33 (d, J=7.5 Hz, 1H, ArH), 3.97 (s, 3H, −OCH_3, 3.89−3.84 (m, 2H, N−CH_2), 2.30−2.08 (m, 4H, CH_2), 1.94−1.88 (m, 2H, CH_2), 1.60−1.53 (m, 2H, CH_2), 1.07−1.02 (m, 9H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 194.8, 190.1, 177.8, 160.6, 154.7, 152.8, 143.8, 136.9, 134.9, 133.2, 131.4, 130.9, 130.8, 130.4, 129.5, 128.2, 122.5, 121.6, 121.3, 121.0, 115.2, 115.0, 114.8, 110.4, 107.8, 55.7, 50.1, 47.4, 41.3, 40.3, 32.2, 29.4, 28.9, 26.6, 20.4, 13.8; Anal. Calcd for $C_{36}H_{36}N_2O_3$ C 77.12, H 6.47, N 5.00; found C 77.25, H 6.46, N 5.07%.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures for synthesis of spiro[indolo-3,10′-indeno[1,2-*b*]quinolin]-2,9′,11′-triones derivatives, scale up reaction and spectral data, copies of ^{1}H and ^{13}C NMR spectra, and IR analysis data of all the new synthesized compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscombsci.5b00038.

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Notes

The authors declare no competing financial interest.

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