La(OTf)$_3$-catalyzed, three-component synthesis of spiro[Indolo-3,10'-indeno[1,2-b]quinolin]-2,4,11'-triones in PEG-400 under conventional heating and ultrasonic irradiation

Sudesh Kumari, M. Rajeswari, and J. M. Khurana

Department of Chemistry, University of Delhi, Delhi, India

ABSTRACT
An efficient La(OTf)$_3$-catalyzed three-component reaction has been developed for the synthesis of highly substituted spiro[indolo-3,10'-indeno[1,2-b]quinolin]-2,4,11'-triones in polyethylene glycol (PEG-400) under conventional heating and ultrasonic irradiation. The most exciting feature of this methodology is its mechanism involving the unusual ring opening of an isatin moiety followed by recyclization. All the reactions resulted in good yield of products. The important features of this reaction are use of green solvent, good yields, less reaction times, and recyclability of the catalyst.

GRAPHICAL ABSTRACT

ARTICLE HISTORY
Received 1 September 2015

KEYWORDS
La(OTf)$_3$; multicomponent reactions (MCRs); PEG-400; spirooxindole; ultrasonic irradiation

Introduction
Design and synthesis of heterocyclic compounds having structural complexity and diversity is a major challenge for organic and medicinal chemists. Multicomponent reactions (MCRs) provide molecular diversity, require short reaction times, and give better yields compared to multiple-step syntheses, thus reducing the consumption of energy and manpower. Nitrogen-containing five-membered heterocyclic compounds have played an important role in the field of medicinal chemistry. These heterocyclic compounds with spirooxindole framework are endowed with a wide range of biological activities such as analgesic, fungicidal, antidepressant, antitumor, antimicrobial, antimalarial, and antibacterial. Similar types of multicomponent reactions have been reported with different methods, e.g., synthesis of pyrrolo[2,3,4-kl]acridin-1-one by using L-proline as catalyst.
in toluene under reflux,\textsuperscript{[5]} synthesis of acridine/indole pairs via Brønsted acid–promoted domino reaction,\textsuperscript{[6]} synthesis of 4-arylacridinediones,\textsuperscript{[7]} and synthesis of spiro[indolo-3,10′-inden-1,2-b]quinolin]-trione using FeCl$_3$ as catalyst.\textsuperscript{[8]}

Regarding the utility of carrying out the synthesis of spirocyclic compounds under green chemical conditions, we had to avoid the use of volatile and poisonous organic solvents. Polyethylene glycol (PEG-400) and modified polyethylene glycol derivatives have become more popular alternate reaction media, because of their interesting properties such as non-toxicity, biocompatibility, and biodegradability when compared to other neoteric solvents such as ionic liquids, supercritical fluids, and micellar systems.\textsuperscript{[9]} Therefore, PEG-400 can be safely used as an ideal green solvent for the synthesis of our target organic compounds.

Taking into account the effect of all these advantages and our continued interest in the development of new, green, and efficient synthetic methodologies,\textsuperscript{[10]} we developed an efficient method for synthesis of spiro[indolo-3,10′-inden-1,2-b]quinolin]-2,4,11′-triones using lanthanum triflate as catalyst under green conditions. Lanthanum triflate has received considerable attention as an inexpensive, nontoxic, readily available, and recyclable catalyst for various transformations under mild conditions. There are several advantages of this particular catalytic system for the improvement of the reaction rate and various reaction conditions (like temperature, pressure, etc.) to reduce the use of costly anhydrous or aprotic hazardous organic solvents. Recently Mondal et al. have reported synthesis of spiro compounds containing oxindole and indene moieties using cetyl trimethyl ammonium bromide (CTAB) as a catalyst under refluxing for 4–6 h.\textsuperscript{[11]} The main disadvantage of this method is long reaction times.

**Results and discussion**

We present herein an efficient and environmentally benign protocol for the synthesis of spiro[indolo-3,10′-inden-1,2-b]quinolin]-2,4,11′-triones (4a–4v) by one-pot, three-component condensation of 1,3-indandione (1), isatins (2), and enamines (3) in a ratio of 1:1:1 using La(OTf)$_3$ as catalyst in PEG-400 at 40 °C and also under ultrasonic irradiation. The reactions are complete in ∼30 min under conventional heating at 40 °C and in ∼10 min under ultrasonic irradiation.

The optimization for the reaction was evolved after attempting the model reactions of 3-(4-chlorophenylamino)-5,5-dimethylcyclohex-2-enone (1.0 mmol), 1,3-indandione (1.0 mmol), and 5-nitrosatin (1.0 mmol) in different solvents and catalysts (Scheme 1). The synthesis of starting material 3-(4-chlorophenylamino)-5,5-dimethylcyclohex-2-enone (functionalized enamines) was carried out by reaction of dimeredone (1.0 mmol) and

![Scheme 1. Synthesis of spiro compound 4a.](image-url)
substituted aniline (1.0 mmol) in the presence of acetic acid in ethanol under reflux. The three-component reaction of 3-(4-chlorophenylamino)-5,5-dimethylcyclohex-2-enone (1.0 mmol), 1,3-indandione (1.0 mmol), and 5-nitroisatin (1.0 mmol) was first attempted in ethanol using La(OTf)₃ (20 mol%) as catalyst at 40 °C (Table 1, run 1). The reaction was incomplete after 200 min and formation of a new product was observed. The reaction was quenched and the product separated. The product was identified as 1′-(4-chlorophenyl)-6′,6′-dimethyl-8-nitro-6′,7′-dihydrospiro[indeno[1,2-b]quinoline-10,3′-indole]-2′,4′,11(1′H,5H,5′H)-trione (4a) (27%) by IR, ¹H NMR, ¹³C NMR, distortionless enhancement by polarization transfer (DEPT), and high-resolution mass spectrometry (HRMS) spectra.

The model reaction was then attempted in different solvents such as methanol, acetonitrile, ethylene glycol, PEG-400, and PEG-600 under otherwise identical reaction conditions (Table 1, runs 2–6). Reactions in methanol and acetonitrile were incomplete after 240 min and 180 min, respectively, yielding only 30 and 25% of 4a (Table 1, runs 2, 3). The reaction attempted in ethylene glycol was complete after 100 min but yielded only 42% of 4a (Table 1, run 4). The reactions attempted using PEG-400 and PEG-600 as solvent under otherwise identical reaction conditions were complete in 30 and 40 min, and yielded 95% and 78% of 4a, respectively (Table 1, runs 5, 6). This reaction repeated in PEG-400 in the absence of catalyst yielded only 55% of 4a after 300 min (Table 1, run 7), while the reaction using 10 mol% of catalyst yielded 80% of 4a after 50 min (Table 1, run 8).

We also explored the application of CAN and FeCl₃ as catalysts in PEG-400 (Table 1, runs 9, 10). These reactions yielded only 60% and 46% of 4a, respectively. The reaction was also attempted under ultrasonic irradiation. The reaction was complete in 10 min and resulted in 94% of 4a (Table 1, run 11).

Encouraged by these results, we investigated the scope of the reaction of 1,3-indandione (1) with different isatins (2) and enamines (3) under optimized reaction conditions. All the reactions were complete in 25–35 min under conventional heating at 40 °C and in 7–10 min under ultrasonic irradiations at room temperature and gave the corresponding products in good yields by a simple workup. (Scheme 2). The results are compiled in Table 2.

The structure of 4a was elucidated using NMR (¹H, ¹³C), IR, DEPT, and HRMS spectra. Various characteristic signals are shown in Fig. 1.

| Entry | Solvent           | Catalyst        | Mol% of catalyst | Temp (°C) | Time (min) | Yield (%) |
|-------|-------------------|-----------------|------------------|-----------|------------|-----------|
| 1     | EtOH              | La(OTf)₃       | 20               | 40        | 200        | 27        |
| 2     | MeOH              | La(OTf)₃       | 20               | 40        | 240        | 30        |
| 3     | CH₃CN             | La(OTf)₃       | 20               | 40        | 180        | 25        |
| 4     | Ethylene glycol   | La(OTf)₃       | 20               | 40        | 100        | 42        |
| 5     | PEG-400           | La(OTf)₃       | 20               | 40        | 30         | 95        |
| 6     | PEG-600           | La(OTf)₃       | 20               | 40        | 40         | 78        |
| 7     | PEG-400           | La(OTf)₃       | 10               | 40        | 30         | 55        |
| 8     | PEG-400           | La(OTf)₃       | 20               | 40        | 120        | 60        |
| 9     | PEG-400           | CAN             | 20               | 40        | 90         | 46        |
| 10    | PEG-400           | FeCl₃           | 20               | 40        | 10         | 94        |
| 11    | PEG-400           | La(OTf)₃       | 20               | RT        |            |           |

aReaction of 1,3-indandione (1.0 mmol), 5-nitroisatin (1.0 mmol), and 3-(4-chlorophenylamino)-5,5-dimethylcyclohex-2-enone (1.0 mmol).
bIncomplete reaction.
cReaction was performed under ultrasonic irradiation at room temperature.
The $^1$H NMR spectrum of 4a revealed two sharp singlets at $\delta$ 0.97 and 1.03 due to the methyl protons. The four methylene protons appeared as multiplets in a range of $\delta$ 2.79–2.00. Eleven aromatic protons appeared in the range of $\delta$ 8.17–7.34. There is one singlet at $\delta$ 11.52 for one N-H proton. Further, the off-resonance decoupled $^{13}$C NMR of 4a exhibited signals at $\delta$ 27.4 and 29.3 due to two methyl carbons and at $\delta$ 34.1 and 49.0 for two quaternary carbons. Two methylene carbons have signals at $\delta$ 36.1 and 51.1. The signals at $\delta$ 179.16, 189.06, and 190.48 are due to three carbonyl carbons. The carbonyl group 1 is in conjugation with double bond, showing C-13 value at $\delta$ 190.48, while carbonyl group 2 has more conjugation with double bond and aromatic ring, so C-13 value is somewhat less at $\delta$ 189.06. The carbonyl carbon of amide group appears in the range of 160–180 ppm due to conjugation with lone pair of nitrogen atom and hence the amidic carbonyl group 3 shows C-13 value at $\delta$ 179.16. The 20 aromatic carbons and two olefinic carbons appeared in the range of $\delta$ 118.31–160.17. The position of peaks for methyl, methylene, methane, and quaternary carbons were assigned by DEPT spectra of compound 4a. IR spectra of the compound 4a showed peaks at 1670 cm$^{-1}$ (carbonyl stretch), 1548 cm$^{-1}$.

**Scheme 2.** Synthesis of spiro[indolo-3,10'-indeno[1,2-b]quinolin]-2,4,11'-triones (4a–4v).

**Table 2.** Synthesis of spiro[indolo-3,10'-indeno[1,2-b]quinolin]-2,4,11'-triones (4a–4v)a.

| Product | $R_1$ | $R_2$ | $R_3$ | Method A | Method B |
|---------|-------|-------|-------|----------|----------|
|         | Time (min) | Yield (%) | Time (min) | Yield (%) |
| 4a      | 30     | 95     | 10     | 94       |
| 4b      | 30     | 90     | 9      | 90       |
| 4c      | 35     | 87     | 10     | 88       |
| 4d      | 30     | 88     | 10     | 90       |
| 4e      | 30     | 92     | 10     | 91       |
| 4f      | 30     | 85     | 8      | 87       |
| 4g      | 30     | 90     | 10     | 90       |
| 4h      | 30     | 93     | 10     | 90       |
| 4i      | 35     | 89     | 10     | 88       |
| 4j      | 30     | 87     | 9      | 89       |
| 4k      | 30     | 85     | 10     | 87       |
| 4l      | 25     | 94     | 7      | 95       |
| 4m      | 30     | 93     | 8      | 94       |
| 4n      | 25     | 96     | 10     | 95       |
| 4o      | 25     | 93     | 10     | 92       |
| 4p      | 30     | 95     | 9      | 92       |
| 4q      | 25     | 94     | 7      | 95       |
| 4r      | 25     | 92     | 7      | 90       |
| 4s      | 30     | 90     | 9      | 91       |
| 4t      | 30     | 95     | 10     | 94       |
| 4u      | 30     | 96     | 10     | 94       |
| 4v      | 25     | 86     | 7      | 87       |

aReaction of 1,3-indandione (1) (1.0 mmol), isatins (2) (1.0 mmol), and enamiones (3) (1.0 mmol) in presence of La(OTf)$_3$ in PEG-400 at 40°C and under ultrasonic radiations.
(asymmetric –NO₂ stretch), and 1332 cm⁻¹ (symmetric –NO₂ stretch). The mass spectrum of 4a showed a molecular ion peak at m/z 552.1317 [M+H]⁺.

A probable mechanism involved in the formation of products is outlined in Scheme 3. The most exciting feature of mechanism is the unusual ring opening of an isatin moiety. At first, the nucleophilic addition reaction occurs between the enaminoine (3) with the more electrophilic carbonyl center of isatin (2) in Lewis acid medium (La³⁺ binds with

**Figure 1.** Various characteristic ¹H and ¹³C NMR peaks of 4a.

**Scheme 3.** Proposed mechanism for the synthesis of 4.
carbonyl oxygen of isatin (2) and enhances the electrophilic nature) to give an imine species (5) that tautomerizes to yield an intermediate (6). This intermediate 6 undergoes intramolecular cyclization to form the intermediate 7, which is immediately converted to a more reactive and unstable intermediate 8 via ring opening of indoline-2,3-dione. Isatin is reported to undergo ring opening in the presence of a base such as dimethyl amine or nucleophile. In the proposed mechanism, the ring opening takes place by nucleophilic attack of nitrogen to amidic carbonyl carbon of isatin. Because of the high reactivity, intermediate 8 instantly undergoes further nucleophilic addition with a molecule of 1,3-indandione (1) to produce another imine intermediate (9), which tautomerizes to yield 10. Finally, the intramolecular cyclization of 10 results in the ultimate spiro compound (4) via tautomerization of 11. The most observable feature is the formation of a more essential intermediate (8), because it is the key intermediate for the final product.

A reaction has also been carried out with allyl isatin under otherwise identical conditions. This condensation gives 1'-allyl-7,7-dimethyl-5-p-methyl-7,8-dihydrospiro[indeno[1,2-b]quinoline-10,3'-indoline]-2',9,11(5H,6H)-trione (4w) as the isolated product as identified by spectral data and reported earlier. The reaction does not involve ring opening.

We also examined the recyclability of the catalyst and solvent system under ultrasonic irradiation. The recyclability of the La(OTf)$_3$–PEG-400 system was tested by six recycling experiments. The substrates were also changed from one cycle to another. The substrates chosen resulted in the synthesis of 4a, 4h, 4m, 4n, 4o, and 4r. The product was separated from the reaction mixture by simple filtration. This allows quick recovery of catalyst and solvent for reuse in the next run. The results of recycling experiment are shown in Fig. 2. All reactions were complete in 10–19 min and afforded the products in 81–94% yield. The catalyst showed no substantial reduction in activity. Therefore, this system acts as an excellent recyclable reaction medium for synthesis of spiro[indolo-3,10'-indenol[1,2-b]quinolin]-2,4,11'-triones (4a–4v).

**Conclusion**

We have reported an efficient methodology for the synthesis of substituted spiro[indolo-3,10'-indenol[1,2-b]quinolin]-2,4,11'-triones by a three-component, one-pot reaction of
1,3-indandione (1), isatins (2), and enamiones (3) using La(OTf)$_3$ as catalyst in PEG-400 at 40 °C under conventional heating and ultrasonic irradiations. This protocol offers advantages in terms of atom economy, easy workup, green reaction media, good yields, less reaction time, and recyclability of catalyst without any significant loss in catalytic activities.

**Experimental**

Structures of all of the compounds were identified by their spectral data. Precoated aluminium plates with silica gel 60 F254 from Merck were used to monitor reaction progress. Ultrasonic bath (54 KHz, 300 W, 3-L capacity) from Throughclean Ultrasonic Pvt. Ltd. (India) was used for reactions. Melting points were determined on a Buchi melting-point M-560 apparatus and are uncorrected. IR (KBr) spectra were recorded on Perkin-Elmer FTIR spectrophotometer and the values are expressed as _ν_ max cm$^{-1}$. The $^1$H NMR and $^{13}$C NMR spectra were recorded on Jeol JNM ECX-400P at 400 MHz and 100 MHz respectively. Mass spectra were recorded at Bruker Micro TOF Q-II. The chemical shift values are recorded on δ scale. The enamiones were prepared by the reported method.[12]

**General procedure for the synthesis of spiro[Indolo-3,10′-indenox[1,2-b]quinolin]-2,4,11′-triones (4a–4 t) under conventional heating conditions (method A)**

A mixture of 1,3-indandione (1) (1.0 mmol), isatin (2) (1.0 mmol), enamione (3) (1.0 mmol), and La(OTf)$_3$(20 mol%) in PEG-400 (5 mL) was placed in a 50-mL, round-bottomed flask which was stirred at 40 °C on a preheated oil bath for an appropriate time as shown in Table 2. After completion of the reaction as monitored by thin-layer chromatography (TLC; ethyl acetate/petroleum ether, 40:60 v/v), the reaction mixture was cooled to room temperature and quenched with ice. The precipitated product was filtered at pump and dried. The products so obtained were purified either by flash column chromatography (4b–4 g, 4i–4k) over silica gel (230–400 mesh) or by recrystallization (4a, 4 h, 4l–4 t) to afford pure products. All the products were characterized using $^1$H NMR, $^{13}$C NMR, IR, and mass spectra.

**General procedure for the synthesis of spiro[Indolo-3,10′-indenox[1,2-b]quinolin]-2,4,11′-triones (4a–4 t) under ultrasonic irradiation (method B)**

A mixture of 1,3-indandione (1) (1.0 mmol), isatin (2) (1.0 mmol), enamione (3) (1.0 mmol), and La(OTf)$_3$(20 mol%) in PEG-400 (5 mL) was placed in a 50-mL, round-bottomed flask which was sonicated at room temperature for appropriate time as shown in Table 2. After completion of the reaction as monitored by TLC (ethyl acetate/petroleum ether, 40:60 v/v), the reaction mixture was cooled to room temperature and quenched with ice. The precipitated product was filtered at pump and dried. The products so obtained were purified either by flash column chromatography (4b–4 g, 4i–4k) over silica gel (230–400 mesh) or by recrystallization (4a, 4 h, 4l–4 t) to afford pure products. All the products were characterized using $^1$H NMR, $^{13}$C NMR, IR, and mass spectra.
Funding

S. K. and R. M. thank the Council of Scientific and Industrial Research, New Delhi, India, for the awards of Junior Research Fellowship/Senior Research Fellowship.

References

[1] Trost, B. M. Angew Chem. Int. Ed. Engl. 1995, 34, 259–281.
[2] (a) Marson, C. M. Chem. Soc. Rev. 2012, 41, 7712–7722; (b) Singh, M. S.; Chowdhury, S. RSC Adv. 2012, 2, 4547–4592; (c) Zhu, J. P.; Bienayme, H. Multicomponent Reactions; Wiley-VCH: Weinheim, Germany, 2005; (d) Ganem, B. Acc. Chem. Res. 2009, 42, 463–472; (e) Domling, A. Chem. Rev. 2006, 106, 17–89.
[3] (a) Balme, G.; Bossharth, E.; Monteiro, N. Eur. J. Org. Chem. 2003, 4101–4111; (b) Zhu, J. Eur. J. Org. Chem. 2003, 7, 1133–1144.
[4] (a) Joshi, K. C.; Dandia, A.; Baweja, S.; Joshi, A. J. Heterocycl. Chem. 1989, 26, 1097–1099; (b) Jones, G.; Rae, W. J. Tetrahedron 1966, 22, 3021–3026; (c) Sundberg, R. J. The Chemistry of Indoles; Academic: New York, 1996.
[5] Wang, H.; Li, L.; Lin, W.; Xu, P.; Huang, Z.; Shi, D. Org. Lett. 2012, 14, 4598–4601.
[6] Jiang, B.; Wang, X.; Li, M. Y.; Wu, Q.; Ye, Q.; Xu, H. W.; Tu, S. J. Org. Biomol. Chem. 2012, 10, 8533–8538.
[7] Wang, G. W.; Miao, C. B. Green Chem. 2006, 8, 1080–1085.
[8] Mondal, A.; Mukhopadhyay, C. ACS Comb. Sci. 2015, 17, 404–408.
[9] Chen, J.; Spear, S. K.; Huddleston, J. G.; Rogers, R. D. Green Chem. 2005, 7, 64–82.
[10] (a) Khanna, G.; Chaudhary, A.; Khurana, J. M. Tetrahedron Lett. 2014, 55, 6652–6654; (b) Sindhu, J.; Singh, H.; Khurana, J. M. Mol. Divers. 2014, 18, 345–355; (c) Singh, H.; Sindhu, J.; Khurana, J. M.; Sharma, C.; Aneja, K. R. RSC Adv. 2014, 4, 5915–5926; (d) Singh, H.; Sindhu, J.; Khurana, J. M. RSC Adv. 2013, 3, 22360–22366; (e) Saluja, P.; Chaudhary, A.; Khurana, J. M. Tetrahedron Lett. 2014, 55, 3431–3435; (f) Khurana, J. M.; Chaudhary, A.; Lumb, A.; Nand, B. Green Chem. 2012, 14, 2321–2327; (g) Khurana, J. M.; Chaudhary, A.; Nand, B.; Lumb, A. Tetrahedron Lett. 2012, 53, 3018–3022; (h) Singh, H.; Sindhu, J.; Khurana, J. M.; Sharma, C.; Aneja, K. R. Eur. J. Med. Chem. 2014, 77, 145–154; (i) Rajeswari, M.; Sindhu, J.; Singh, H.; Khurana, J. M. RSC Adv. 2015, 5, 39686–39691; (j) Singh, H.; Kumari, S.; Khurana, J. M. Chin. Chem. Lett. 2014, 25, 1336–1340; (k) Sindhu, J.; Singh, H.; Khurana, J. M.; Sharma, C.; Aneja, K. R. Chin. Chem. Lett. 2015, 26, 50–54; (l) Kumari, S.; Sindhu, J.; Khurana, J. M. Synth. Commun. 2015, 45, 1101–1113.
[11] Mondal, A.; Brown, M.; Mukhopadhyay, C. RSC Adv. 2014, 4, 36890–36895.
[12] Cui, B.; Wang, R. H.; Chen, L. Z.; Jin, Y.; Han, G. F. Synth. Commun. 2011, 41, 1064–1070.
[13] Bergman, J.; Stalhandske, C.; Vallberg, H. Acta Chem. Scand. 1997, 51, 753–759