Tetrahedron Letters 53 (2012) 3497–3501

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A novel one-pot synthesis of spiro[indoline-3,4′-pyrazolo[3,4-*e*][1,4]thiazepine] diones using recyclable bioglycerol-based sulfonic acid functionalized carbon catalyst

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ARTICLE INFO

Article history:
Received 12 March 2012
Revised 26 April 2012
Accepted 27 April 2012
Available online 2 May 2012

Keywords:
Bioglycerol-based carbon catalyst
1,4-Thiazepine
Spirooxindole
Isatin
Amino pyrazole
2-Mercapto acetic acid

ABSTRACT

A novel, simple, and efficient synthetic protocol has been developed for the synthesis of spiro[indoline-3,4′-pyrazolo[3,4-*e*][1,4]thiazepine] diones, by using bioglycerol-based sulfonic acid functionalized carbon as a recyclable catalyst, devoid of moisture sensitive metal catalysts and corrosive acidic reagents. This new protocol produces novel heptacyclic spirooxindole derivatives in good to excellent yields, with operational simplicity and recycling of the catalyst in comparison to predictable pentacyclic compounds. The catalyst can be prepared by a simple adoptable procedure from an inexpensive and readily available bio-glycerol and found to be recoverable and reusable up to four cycles without any loss of activity.

Drug design and development have been accomplished with iterative manipulation of individual structures with the aid of fundamental chemical reactions. Multi-component reaction (MCR) strategy is a significant approach utilized by researchers globally to create combinatorial libraries of molecules containing different pharmacophoric components, which are responsible for diverse biological activities.[1] Multi-component condensations differ from multi-step processes and are efficient in the modern drug discovery and development. In the past decade, there has been tremendous development in three- and four-component reactions.[2]

Heterocycles containing 1,4-thiazepine fragment are a key moiety in a large number of natural and synthetic bio-active molecules. Among them, aryl- and heteroaryl-fused derivatives of thiazepine represent an important group of compounds with interesting pharmaceutical properties. Some of these compounds exhibited angiotensin-converting enzyme inhibition,[3] leading to the development of temocapril,[4] a drug used for the treatment of hypertension.

Very recently, some thiazepinones have shown nanomolar affinity for a specific domain of a tyrosine kinase enzyme, the Src SH2, following structure-based rational drug design.[5] Different alkyl derivatives of 3,4-dihydro-5-oxo-1,4-benzothiazepine were also described as calcium channel antagonists, HIV-1 enzyme integrase and reverse transcriptase inhibitors, and antitumor agents.[6] Numerous heteroannulated bioisosteric analogs of this core fragment were reported as potent inhibitors of Herpes simplex virus type 1 (HSV-1) replication, compounds possessing H1 antihistamine activity, dopamine D2 receptors, and selective antagonists of 5-HT1A and vasoconstrictor agents.[7] Compounds from different 1,4-benzothiazepine type structural classes, such as CGP37157 and diltiazem have been reported to inhibit mNCE activity (Fig. 1).[8] CGP37157 is the most potent inhibitor for mNCE, with a reported IC_{50} of 0.4 μM.

The spirooxindole system is one of the prominent heterocycles found in numerous natural and synthetic products, with useful pharmaceutical activities.[9] For example, spirotryprostatin A, a natural alkaloid isolated from the fermentation broth of *Aspergillus fumigatus*, has been identified as a novel inhibitor of microtubule assembly,[10] and pteropodine and isopteropodine have been shown to modulate the function of muscarinic serotonin receptors.[11] They have been shown to exhibit local anesthetic properties. The unique structural array and the highly pronounced pharmacological activity displayed by the class of spirooxindoles have made them attractive synthetic targets (Fig. 1).

Thia-azaheterocycles gained prominence because of their extensive biological and pharmacological activities.[12] Several methods have been reported for the preparation of spirooxindole derivatives connecting the thioacid synthon.[13] Recently Shi et al., reported

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http://dx.doi.org/10.1016/j.tetlet.2012.04.122

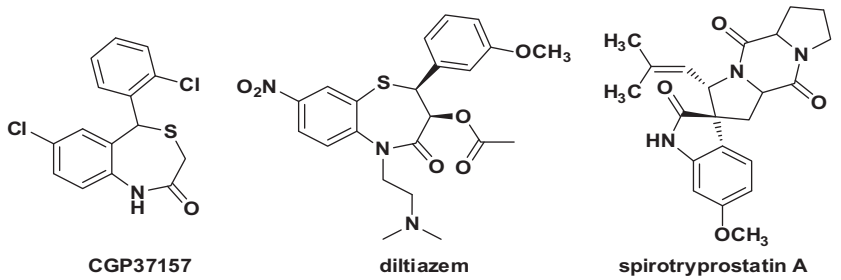
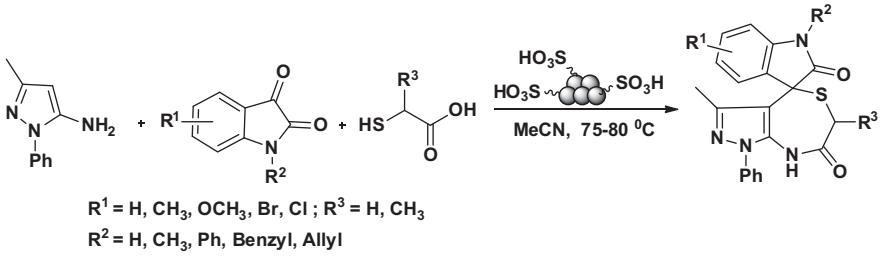


Figure 1. Biologically active benzothiazepines and spirooxindole.



Scheme 1. Synthesis of spiro[indoline-3,4′-pyrazolo[3,4-*e*][1,4]thiazepine] dione.

novel heptacyclic spirooxindole derivatives by using *p*-TSA as a catalyst.[14]

Despite the importance of these reported protocols many suffer from drawbacks such as use of expensive reagents, harsh reaction conditions, prolonged reaction times, cumbersome product isolation procedures, and low yields as well as more than stoichiometric amount of catalyst. Hence, to explore a mild, efficient and environmentally benign recyclable synthetic protocol for the spiro[indoline-3,4′-pyrazolo[3,4-*e*][1,4]thiazepine] diones is highly desirable.

In recent years, carbon-based solid acid catalysts[15] have gained prominence, due to their significant advantages over the homogeneous catalytic systems such as increased activity, selectivity, longer catalyst life, negligible equipment corrosion, ease of product separation, and reusability. Prabhavathi et al., reported sulfonic acid-functionalized polycyclic aromatic carbon catalyst from bio-glycerol (biodiesel by-product) and also from the glycerol-pitch (waste from fat splitting industry) by the in situ partial carbonization and sulfonation in a single pot[16] and studied carbon-based bio-glycerol solid acid catalyst[†]applications.[17] In continuation of interest in the development of novel heterocyclic compounds[18] and exploring the possible applications for the carbon-based bio-glycerol solid acid catalyst, herein, we report a facile and efficient one-pot synthesis of spiro[indoline-3,4′-pyrazolo[3,4-*e*][1,4]thiazepine] diones for the first time (Scheme 1), catalyzed by the inexpensive, highly stable, robust, and recyclable bio-glycerol based solid acid, which can be easily produced from the naturally available bio-glycerol.

Initially, a model reaction was conducted by reacting isatin (1.0 mmol), 5-amino-3-methylpyrazole (1.0 mmol), and 2-mercapto acetic acid (1.0 mmol) in polyethylene glycol (PEG-400) at a temperature of 100–110 °C, but the reaction did not yield the desired product, and starting materials were recovered back. However, the same reaction was studied using bioglycerol-based carbon acid as a catalyst, at room temperature, affording the desired spiro[indoline-3,4′-pyrazolo[3,4-*e*][1,4]thiazepine]-dione in a moderate yield (47%). Based on this interesting result, further optimization of this reaction is explored. The progress of the reaction was studied at different reaction temperatures and it has been observed that 75–80 °C is the optimum temperature for obtaining good yields.[19] To expand the scope of this method, a variety of substituted isatins were used in this reaction process, resulting in a range of varied spiro[indoline-3,4′-pyrazolo[3,4-*e*][1,4]thiazepine] dione. Isatins with both electron donating or electron withdrawing substituents reacted very well, affording moderate to high yields of spiro[indoline-3,4′-pyrazolo[3,4-*e*][1,4]thiazepine] diones and results are tabulated in Table 1. The isatins containing the electron donating groups such as methyl and methoxy at 5-position produced the products in high yields (Table 1, entries 3, 4, 5, and 6). Yields were moderate with halogen substituted isatins (Table 1, entries 7, 8, 9, and 10). Reaction was also conducted with N-substituted isatins (Table 1, entries 11–18).

The scope of this protocol was extended a step further, using 2-mercaptopropanoic acid in place of the 2-mercaptoacetic acid component, providing the desired spiro[indoline-3,4′-pyrazolo [3,4-*e*][1,4]thiazepine] diones in good yields (Table 1, entries 2, 4, 6, and 8).

The recyclability of the catalyst, was also demonstrated. The reaction mixture was allowed to cool and the catalyst was recovered by simple filtration, washed with ethyl acetate and acetone, and dried under reduced pressure. The catalyst was reused for the same reaction without further activation. The reaction proceeded smoothly even after three cycles, without any extension of reaction time or marked loss in yield (Table 2).

The recyclability of the bioglycerol-based carbon catalyst was examined by using isatin (1.0 mmol), 5-amino-3-methyl-1-phenyl-pyrazole (1.0 mmol), and 2-mercaptoaceticacid (1.0 mmol) in MeCN (10 mL), as a model reaction. We proposed a plausible mechanism for the synthesis of spiro[indoline-3,4′-pyrazolo[3,4-*e*][1,4]thiazepine] diones in Scheme 2. At first, isatin forms Baylis–Hillman type adduct (A) by the nucleophilic addition with 5-amino-3-methyl-1-phenyl-pyrazole. This is a key intermediate, which on further dehydration produces the intermediate (B), which on further Michael addition with thioacid followed by dehydration forms the desired product (C).

In conclusion, we have demonstrated a mild and highly efficient protocol for the synthesis of spiro[indoline-3,4′-pyrazolo[3,

[†] The bioglycerol based sulfonic acid carbon reagent is not commercially available but prepared by following the reported procedure cited in the Ref. 16.

Table 1
Synthesis of spiro[indoline-3,4′-pyrazolo[3,4-*e*][1,4]thiazepine] diones derivatives[a]

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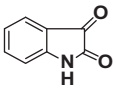
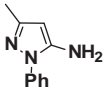
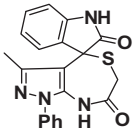
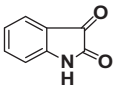
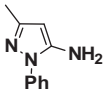
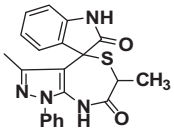
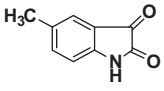
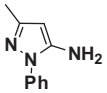
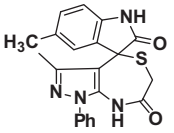
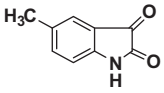
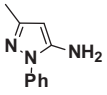
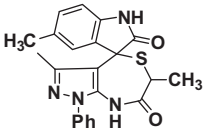
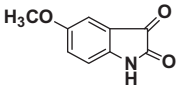
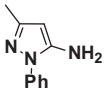
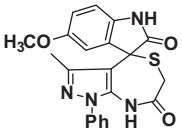
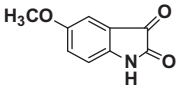
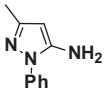
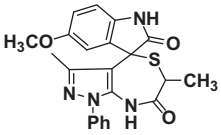
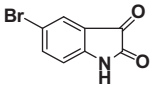
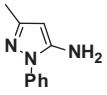
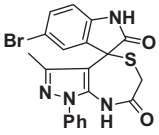
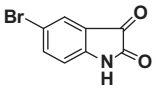
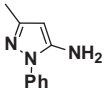
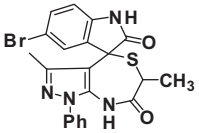
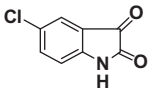
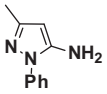
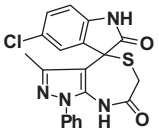
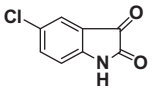
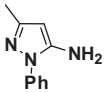
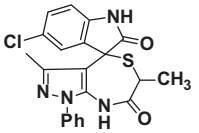
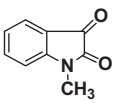
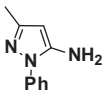
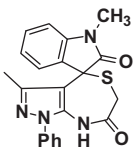
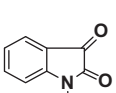
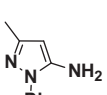
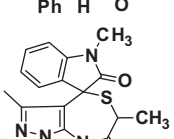
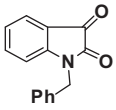
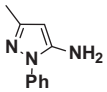
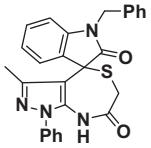
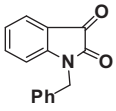
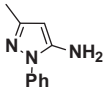
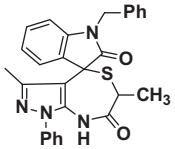
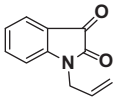
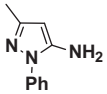
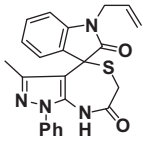
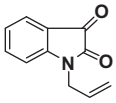
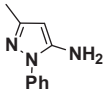
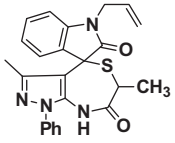
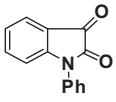
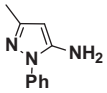
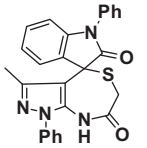
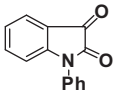
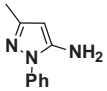
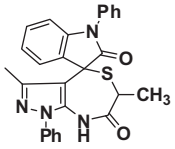
1			H		7	89[18]
2			CH_3		7	86[18]
3			H		7	87[18]
4			CH_3		7	85[18]
5			H		7	91
6			CH_3		7	88
7			H		7.5	79[18]
8			CH_3		7.5	78
9			H		7	77
10			CH_3		7	76[18]
11			H		7	87[18]
12			CH_3		7	86[18]

(*continued on next page*)

Table 1 (*continued*)

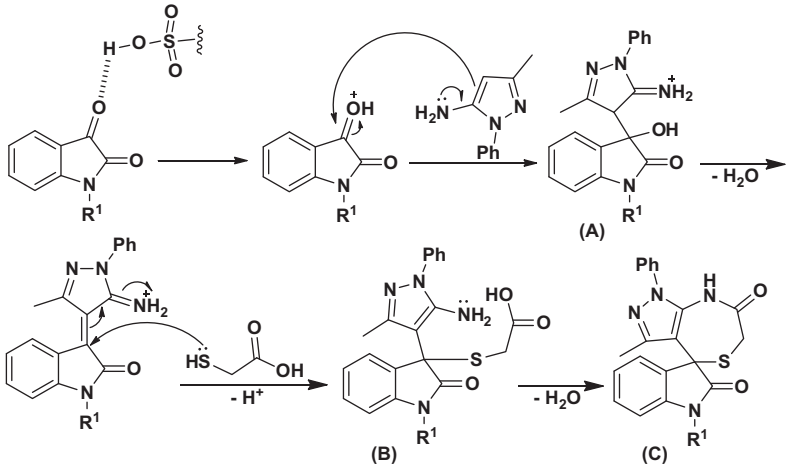
S. No.	Isatin	Pyrazolo amine	R^3	Product	Time (h)	Yeild[b] (%)
13			H		7.5	79
14			CH_3		7.5	77
15			H		8	73
16			CH_3		8	72
17			H		7	82
18			CH_3		7	79

[a] Reaction conditions: Isatin (1.0 mmol), 5-amino-3-methylpyrazole (1.0 mmol), 2-thio aceticcacid (1.0 mmol) and bioglycerol-based carbon catalyst (10 wt% of isatin) at 75–80 °C.
[b] Isolated yields.

Table 2
Recyclability of bioglycerol-based carbon catalyst

Cycles	Yield (%)	Catalyst recovered (%)
Native	90	94
1	87	91
2	84	88
3	82	85

4-*e*][1,4]thiazepine] diones, by using novel recyclable bio-glycerol based carbon catalyst in CH_3CN as a reaction medium. This novel protocol was used to prepare the new heptacyclic spirooxindole derivatives in moderate to good yields. Environmental acceptability, high yields, easy work-up, cleaner reaction profiles, and recyclability of bio-glycerol based carbon catalyst are the important features of this protocol.



Scheme 2. The plausible mechanism for the synthesis of [3,4-*e*][1,4]thiazepine] dione.

Acknowledgments

We thank the CSIR, New Delhi, India, for fellowships to K.K., S.N.M., K.H.V.R., U.C. and UGC for fellowship to K.R.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.04.122.

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19. *General procedure for the synthesis of substituted spiro[indoline-3,4′-pyrazolo[3,4-e][1,4]thiazepine] diones*: To a stirred solution of isatin (1.0 mmol) and 5-amino-3-methylpyrazole (1.0 mmol) in MeCN (10 mL) containing bioglycerol-based carbon catalyst (10 wt% of isatin), 2-thioacid (1.0 mmol) was added and heated to reflux under nitrogen atmosphere at 75–80 °C, until the reaction was complete as indicated by TLC. After completion of the reaction, the catalyst was separated by filtration and washed with ethyl acetate/acetone for reuse. The reaction mixture was concentrated to remove MeCN. After evaporation of the solvent under reduced pressure, the crude residue was extracted with EtOAc and the combined organic layers were washed with brine solution, dried over anhydrous Na_2SO_4, evaporated to get the crude product, which was purified by column chromatography (Silica gel-60), using hexane and EtOAc (80:20) as eluent to give the title compound. *3′-Methyl-1′-phenyl-6′,8′-dihydrospiro[indoline-3,4′-pyrazolo[3,4-e][1,4]thiazepine]-2,7′(1′H)-dione (Table 1, entry 1)*: IR (KBr) 3244, 3109, 2933, 1710, 1650, 1222, 1089 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6, TMS) δ = 10.72 (s, 1H), 9.76 (s, 1H), 7.47–7.54 (m, 4H), 7.40–7.42 (m, 1H), 7.28 (t, J = 7.5 Hz, 1H), 7.16 (d, J = 7.3 Hz, 1H), 6.91–7.03 (m, 2H), 4.70 (d, J = 14.9 Hz, 1H), 3.06 (d, J = 14.9 Hz, 1H), 1.53 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6, TMS) δ 177.7, 170.7, 146.6, 141.0, 137.9, 136.4, 129.3, 128.6, 127.8, 127.2, 124.7, 124.4, 122.1, 109.9, 105.3, 48.1, 29.8, 11.7 ppm. ESI-MS: 377 $(M+H)^+$; $C_{20}H_{17}N_4O_2S$. *3′,5-Dimethyl-1′-phenyl-6′,8′′-dihydrospiro[indoline-3,4′-pyrazolo[3,4-e][1,4]thiazepine]-2,7′(1′H)-dione (Table 1, entry 3)*: IR (KBr) 3244, 3109, 2933, 1710, 1650, 1222, 1089 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6, TMS) δ = 10.48 (s, 1H), 9.31 (s, 1H), 7.39–7.58 (m, 5H), 7.09 (d, J = 7.9 Hz, 1H), 7.01 (s, 1H), 6.88 (d, J = 7.9 Hz, 1H), 4.77 (d, J = 14.9 Hz, 1H), 3.05 (d, J = 14.9 Hz, 1H), 2.28 (s, 3H), 1.58 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6, TMS) δ 177.8, 170.9, 146.8, 138.4, 137.7, 136.2, 131.5, 129.7, 128.7, 127.6, 127.3, 124.9, 124.8, 109.7, 105.3, 48.2, 29.8, 20.4, 11.8 ppm. ESI-MS: 391 $(M+H)^+$; $C_{21}H_{19}N_4O_2S$.