Tetrahedron 74 (2018) 955–961

Contents lists available at ScienceDirect

Tetrahedron

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

Iodine-promoted three-component reaction for the synthesis of spirooxindoles

Min Zhang**, Wenbo Yang, Min Qian, Ting Zhao, Liuqing Yang, Chunyin Zhu*

School of Chemistry and Chemical Engineering, Jiangsu University, Zhenjiang 212013, PR China

ARTICLE INFO

Article history:
Received 20 September 2017
Received in revised form
27 December 2017
Accepted 2 January 2018
Available online 6 January 2018

Keywords:
Iodine
Multi-component reaction
Isatin
Spirooxindole

ABSTRACT

An iodine-promoted three-component reaction for the construction of spirooxindoles has been developed through the green reaction system of catalytic amount of molecular iodine as an alternative catalyst for Lewis acids. Various substituted isatins were able to react with different cyclic 1,3-dicarbonyls and 4-hydroxyl coumarins through this reaction strategy, which shows good functional group tolerance and efficiency.

© 2018 Elsevier Ltd. All rights reserved.

1. Introduction

Heterocyclic spirooxindoles are highly valuable synthetic frameworks because of their varied biological activities as well as wide-ranging utility as synthetic intermediates.[1] These core structures are found in many pharmacological agents and natural products, for example coerulescine, horsfiline, welwitindolinone A, spirotryprostatin A, elacomine, and alstonisine.[2] As a result, the past decades have witnessed numerous impressive successes for the synthesis of diversely structured spirocyclic oxindoles.[3] For example, organocatalyzed asymmetric annulations of oxindole derivatives provided access to spirocarbocyclic oxindoles in good yields with high diastereo- and enantio-selectivities.[4] Additionally, elegant works on metal-catalyzed domino processes has been reported for the facile construction of spirooxindole derivatives.[5] On the other hand, isatin and its derivatives have been widely applied in multi-component reactions for the preparation of spiroheterocyclic compounds.[6,7] Among these isatin-based multi-component reactions, most of them involve the condensation under harsh conditions like high temperature and microwave irradiation.[8] Given the increasing demand for more environmentally acceptable processes, synthetic methods for spirooxindoles employing mild sustainable reaction conditions are still desirable.

Since the discovery by Hibbert[9] in 1915 that tiny amounts of I_2 (0.01 mol%) can catalyze the conversion of diacetone alcohol into mesityl oxide, molecular iodine (I_2) has been recognized as an effective catalysis for various transformations over the past century.[10] Iodine catalysis has evident advantages over acid catalysis and transition-metal catalysis, as it is water-tolerant, relatively cheap and environmentally benign, thus contributing to waste- and health-hazard minimization and cost efficiency.[11] One fascinating application of iodine catalysis is the synthesis of pharmaceutically important heterocycles, as iodine can avoid the problem of residual metal in transition-metal catalysis. For example, iodine has emerged as an alternative catalyst for Lewis acid in the synthesis of five- and six-membered heterocycles through activation of carbon–carbon multiple bond, carbonyl, imine, enamine, thioamide, and hydrazine.[12] In addition, iodine can also serve as a mediator for oxidative coupling in the synthesis of pyridines,[13] 1,2,4-triazoles,[14] indolines,[15] oxazoles,[16] quinolines,[17] 1,2-fused oxindoles,[18] etc. Herein, we report an iodine-catalyzed three-component reaction for the synthesis of spirooxindole derivatives involving isatin derivatives, cyclic 1,3-dicarbonyls and 4-hydroxyl coumarins as the starting materials.

2. Results and discussion

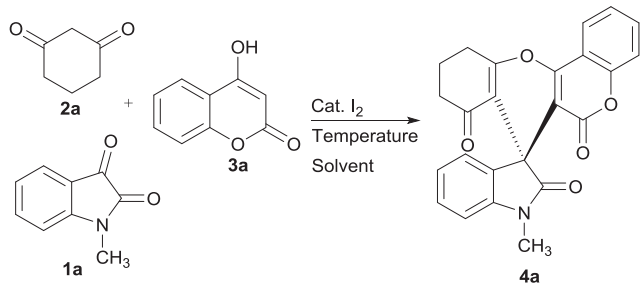
Initially *N*-methylisatin **1a**, 1,3-cyclohexanedione **2a** and 4-hydroxy-2*H*-chromen-2-one **3a** were chosen as the model

* Corresponding author.
** Corresponding author.
E-mail address: 1000004200@ujs.edu.cn (C. Zhu).

https://doi.org/10.1016/j.tet.2018.01.001
0040-4020/© 2018 Elsevier Ltd. All rights reserved.

substrates to study the reaction conditions. At first, different solvents were evaluated employing I_2 (10 mol%) as the catalyst at 60 °C, and no desired product was isolated from the reaction in EtOH, MeOH, THF, dioxane or DME over 72 h (Table 1, entries 1–5). Then it turned out that the desired product could be generated in the reaction using DMF as the solvent, but with a very low yield (8%, Table 1, entry 6). The outcome of the reaction was improved when switching to other aprotic polar solvents like CH_3CN and DMSO (Table 1, entries 7 and 8), and CH_3CN gave a yield up to 61%. Nonpolar solvent, such as toluene, can also work for this transformation and gave a moderate yield (57%, Table 1, entry 9). To our delight, the reaction in $CHCl_3$ under 60 °C gave a yield of 58% (Table 1, entry 10) while a similar yield was obtained from the reaction in CH_2Cl_2, but at lower temperature (40 °C, Table 1, entry 11). This result encouraged us to investigate another chlorine-contained solvent, 1,2-dichloroethane (DCE) and it can give a yield up to 76%, even within shorter reaction time (24 h, Table 1, entry 12). The reaction was further optimized by varying the catalytic amount of iodine and the reaction time. Iodine was found to play a critical role in the outcome of the reaction, as exemplified by the decrease observed in the yield of the reaction as the amount of iodine was reduced from 10 mol% to 5 mol% (Table 1, entry 14). On the other side, increasing the amount of iodine to 20 or 30 mol% also led to inferior outcomes (Table 1, entries 15 and 16), probably due to additional side reaction. As regarding to the reaction temperature, it is found that the reaction would become slower under lower temperature, leading to low conversions and yields, even after extended reaction time (Table 1, entries 17–19). However, higher temperature would also jeopardize the reaction by introducing side reactions that is confirmed by TLC monitoring (Table 1, entries 20–22). So DCE, I_2 (10 mol%) and 60 °C were chosen as the optimized conditions.

Table 1
Optimization of reaction conditions.[a]



Entry	Solvent	I_2 (mol%)	Temperature (°C)	Time (h)	Yield[b] (%)
1	EtOH	10	60	72	N.D.
2	MeOH	10	60	72	N.D.
3	THF	10	60	72	N.D.
4	dioxane	10	60	72	N.D.
5	DME	10	60	72	N.D.
6	DMF	10	60	72	8
7	CH_3CN	10	60	72	61
8	DMSO	10	60	96	24
9	toluene	10	60	96	57
10	$CHCl_3$	10	60	96	58
11	CH_2Cl_2	10	40 (reflux)	96	56
12	**DCE**	**10**	**60**	**24**	**76**
13	DCE	–	60	168	–
14	DCE	5	60	24	63
15	DCE	20	60	24	68
16	DCE	30	60	24	56
17	DCE	10	20	120	45
18	DCE	10	40	72	56
19	DCE	10	50	72	66
20	DCE	10	70	24	68
21	DCE	10	80	24	69
22	DCE	10	90 (reflux)	24	67

Bold signifies the optimized reaction conditions, and they were applied for the synthesis of spirooxindoles.
[a] 0.5 mmol of **1a**, 0.55 mmol of **2a**, 0.55 mmol of **3a**, 2 mL of solvent.
[b] Isolated yield. N.D. = Not detected.

With the optimized conditions in hand, we proceeded to evaluate the scope and generality of this iodine-promoted three-component reaction. Firstly, a wide range of substituted isatins **1** could react with 1,3-cyclohexanedione **2a** and 4-hydroxyl coumarin **3a**, leading to the desired spirooxindole products with moderate to good isolated yields (Scheme 1). Isatins bearing different electron-withdrawing or electron-donating groups at different positions of the benzene ring were all compatible with this reaction (**4a**-**4j**). A series of functional groups, such as nitro, methoxy, and halogen, were all well tolerated under the reaction conditions. In addition to *N*-methylisatins, *N*-benzylisatin and *N*-allylisatin could also undergo this transformation, resulting in the desired products with lower yields (**4k** and **4l**). Moreover, the variation of the coumarin substrate was also possible, as 6-chloro-4-hydroxy-2*H*-chromen-2-one and 7-methoxy-4-hydroxy-2*H*-chromen-2-one could react with *N*-substituted isatin and 1,3-cyclohexanedione under current conditions, leading to spirooxindole product **4l** and **4m**. The complex structure of the spirooxindole products was further confirmed by the X-ray data of **4m** (CCDC number 1813421).

We next examined other cyclic 1,3-dicarbonyl compounds in the three-component reaction with various substituted isatin **1** and 4-hydroxy-2*H*-chromen-2-one **3a**. As showed in Scheme 2, moderate to excellent yields of coupling products were obtained under the optimized conditions using 1,3-cyclopentanedione **2b** and 5,5-dimethylcyclohexane-1,3-dione **2c** as coupling partners (Scheme 2, **4n**-**4y**). Compared to 1,3-cyclohexanedione **2a**, the reactions of 1,3-cyclopentanedione **2b** usually led to lower yields of desired products (**4n**-**4t**), and 5,5-dimethylcyclohexane-1,3-dione **2c** was found to work better for the reaction than simple 1,3-cyclohexanedione **2a**, leading to the generally higher yields of **4u**-**4y**. This phenomenon can be ascribed to the different nucleophilicities of 1,3-diones, which is in the order of **2c** > **2a** > **2b**.[19] As a result, the reaction of *N*-benzylisatin, 5,5-dimethylcyclohexane-1,3-dione **2c** and 4-hydroxy-2*H*-chromen-2-one **3a** proceeded smoothly, leading to the desired product **4x** with a yield up to 91%.

Two mechanisms seem plausible for this transformation (Scheme 3), and they differ in the timing of bond formation. In path a, *N*-methylisatin **1a** is condensed with 1,3-cyclohexanedione **2a** to afford oxoindolylidene **5** followed by addition of 4-hydroxy-2*H*-chromen-2-one **3a** to give intermediate **7**. Subsequent intramolecular acetal formation and dehydration result in the formation of target molecule **4a**. In path b, *N*-methylisatin **1a** reacts with 4-hydroxy-2*H*-chromen-2-one **3a** first, this being followed by the incorporation of 1,3-cyclohexanedione **2a** to generate final product **4a** through similar reactions of path a. During all the courses, iodine is proposed to serve as an alternative catalyst for Lewis acids to activate carbonyl groups.

3. Conclusion

We have developed an iodine-promoted three-component reaction for the synthesis of spirooxindoles. Catalytic amount of molecular iodine was proven to be an effective alternative reaction system for transition-metals in these transformations. Various substituted isatins, cyclic 1,3-dicarbonyls and 4-hydroxyl coumarins undergo this reaction smoothly, leading to the desired products with good functional group tolerance and efficiency.

Download English Version:

https://daneshyari.com/en/article/7827648

Download Persian Version:

https://daneshyari.com/article/7827648

Daneshyari.com