ORGANIC LETTERS

2010
Vol. 12, No. 3
572−575

Multicomponent Reaction Discovery: Three-Component Synthesis of Spirooxindoles

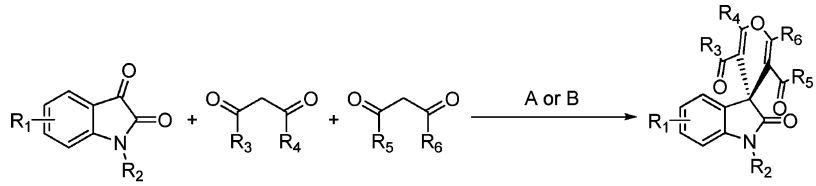
Bo Liang, Srinivas Kalidindi, John A. Porco, Jr., and Corey R. J. Stephenson*

Department of Chemistry and Center for Chemical Methodology and Library Development (CMLD-BU), Boston University, Boston, Massachusetts 02215

crjsteph@bu.edu

Received November 30, 2009

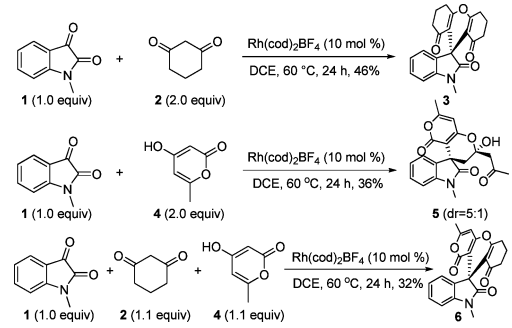
ABSTRACT



The Lewis acid-catalyzed, three-component reaction of isatin and two 1,3-dicarbonyl compounds is reported. Reactions proceed with high efficiency under mild reaction conditions and with good functional group tolerance to afford spirooxindole pyranochromenedione derivatives.

High-throughput screening is an efficient method for discovery of new reactions and synthesis of complex chemotypes.[1] We have recently reported several novel Rh(I)-catalyzed transformations identified using reaction screening in which 1,3-dicarbonyl substrates exhibited diversified reactivities as nucleophiles with electrophiles derived from *o*-alkynylbenzaldehydes.[2] To further explore modes of reactivity of 1,3-dicarbonyl compounds under Rh(I) catalysis, we have screened their reactions with a diverse set of electrophiles. Our analysis led to the discovery of the selective, catalyzed condensation of *N*-methylisatin **1** with two molecules of 1,3-cyclohexanedione **2** to give spirooxindole[3−5] pyranochromenedione **3** in 46% yield (Scheme 1).

Scheme 1. Reactions of *N*-Methylisatin and Various 1,3-Dicarbonyls



Similarly, reaction of 4-hydroxy-6-methyl-2-pyrone **4** with *N*-methylisatin **1** resulted in the production of condensation product **5** in 36% yield (dr = 5:1). The structure of **5** (major

(1) For examples of new reaction development using high-throughput screening, see: (a) Weber, L.; Illgen, K.; Almstetter, M. *Synlett* **1999**, 366. (b) Kana, W. M.; Rosenman, M. M.; Sakurai, K.; Snyder, T. M.; Liu, D. R. *Nature* **2004**, *431*, 545. (c) Miller, S. J. *Nat. Biotechnol.* **2004**, *22*, 1378. (d) Ganem, B. *Acc. Chem. Res.* **2009**, *42*, 463.

(2) Beeler, A. B.; Su, S.; Singleton, C. A.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 1413.

(3) For selected recent examples, see: (a) Castaldi, M. P.; Troast, D. M.; Porco, J. A., Jr. *Org. Lett.* **2009**, *11*, 3362. (b) Zhang, Y.; Panek, J. S. *Org. Lett.* **2009**, *11*, 3366. (c) Shintani, R.; Hayashi, S.-y.; Murakami, M.; Takeda, M.; Hayashi, T. *Org. Lett.* **2009**, *11*, 3754.

(4) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748.

10.1021/ol902764k
Published on Web 01/05/2010

diastereoisomer shown) was confirmed by X-ray crystal structure analysis.[6] Unexpectedly, when **1**, **2**, and **4** were added in a ~1:1:1 ratio in the presence of 10 mol % of $Rh(cod)_2BF_4$ in $Cl(CH_2)_2Cl$ at 60 °C, the three-component coupling product **6** was obtained in 32% after 24 h.[7] Only trace amounts of **3** and **5** were detected along with recovered starting materials. While we were delighted by the selectivity of this three-component reaction, the reaction proceeded very slowly. The isatin was only fully consumed after prolonged reaction time (3 days) affording spirooxindole **6** in 78% yield.

To accelerate the three-component reaction, we next examined additives including Ag(I) salts and observed a significant rate acceleration. Upon further examination, we discovered that the Rh(I) catalyst was not required when $AgBF_4$ was employed as the catalyst, the yield of **6** was improved to 62% (Table 1, entry 2). Consequently, we

Table 1. Optimization of Reaction Conditions for the Formation of **6** from **1**, **2**, and **4**

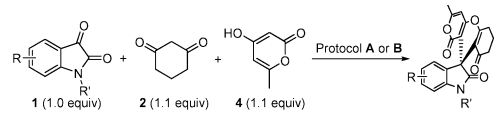
entry[a]	catalyst[b]	time (h)	yield (%)[c]
1	$Rh(cod)_2BF_4$ (10 mol %)	24	32
2	$AgBF_4$ (10 mol %)	24	62
3	$(CuOTf)•C_6H_6$ (10 mol %)	24	38
4	$BF_3•OEt_2$ (10 mol %)	24	65
5	$TiCl_4$ (10 mol %)	24	61
6	$SnCl_4$ (10 mol %)	12	76

[a] Conditions for formation: $Cl(CH_2)_2Cl$, 60 °C; **1** (1.0 equiv), **2** (1.1 equiv), **4** (1.1 equiv). [b] Three-component product is not observed in the absence of catalyst, only **27** (*vide infra*) is observed. [c] Yield (UPLC analysis) using biphenyl as an internal standard.

suspected that the reaction was operating under Lewis acid catalysis. After screening numerous Lewis acids, we found that $SnCl_4$[8] provided the three-component product in good yield after 12 h (Table 1, entry 6), while other catalysts including CuOTf, $BF_3•Et_2O$, and $TiCl_4$ gave low to moderate yields (Table 1, entries 3−5).[9] Other Sn(IV) catalysts and desiccants (4 Å molecular sieves and $MgSO_4$) did not improve the overall efficiency of the transformation.

Subsequent experiments led to the finding that we could further accelerate the three-component reaction to produce spirooxindoles using microwave irradiation. In the event, irradiation of **1**, **2**, and **4** in DCE at 80 °C with 10 mol % of $SnCl_4•5H_2O$ as catalyst afforded an 80% yield of **6** in only 80 min (Table 2, entry 2). As a result of these studies, we examined

Table 2. Three-Component Reaction with Different Isatins



entry	R	R′	protocol[a]	time	product	yield (%)[b]
			A	16 h		63
1	H	H	**B**	80 min	**7**	78
			A	12 h		75
2	H	Me	**B**	80 min	**6**	80
			A	20 h		81
3	H	Ph	**B**	80 min	**8**	56
			A	18 h		81
4	5-OMe	Me	**B**	80 min	**9**	65
			A	18 h		89
5	5-Me	Me	**B**	80 min	**10**	77
			A	18 h		62
6	5-NO_2	Me	**B**	80 min	**11**	85
			A	24 h		75[c]
7	4-Br	Me	**B**	80 min	**12**	52[d]
			A	18 h		90
8	5-Br	Me	**B**	80 min	**13**	80
			A	18 h		93
9	6-Br	Me	**B**	80 min	**14**	84
			A	18 h		65
10	7-Br	Me	**B**	80 min	**15**	67

[a] Protocol A: $SnCl_4$ (10 mol %), $Cl(CH_2)_2Cl$, 60 °C. Protocol B: $SnCl_4•5H_2O$ (10 mol %), $Cl(CH_2)_2Cl$, μW, 80 °C. [b] Isolated yields of compounds purified by chromatography on SiO_2. [c] 20 mol % $SnCl_4$ at 80 °C. [d] 20 mol % $SnCl_4•5H_2O$.

the reaction with a broad range of substrates to determine the reaction specificity and scope. Various substituted isatins were reacted with 1,3-cyclohexanedione **2** and 4-hydroxy-6-methyl-2-pyrone **4** under both thermal and microwave conditions (Table 2). From the results, it is evident that most of the reactions provided the desired spirooxindole products in good to excellent yields employing both electron-deficient (Table 2, entry 6) and electron-rich (Table 2, entry 4) isatins as substrates. Bromo-substitution on the isatin was tolerated including the sterically demanding 4-bromo derivative. In addition, unprotected isatins also participated in the reaction affording the desired coupling product **7** in moderate yield (Table 2, entry 1).

We next examined a number of 1,3-dicarbonyl compounds in the three-component reaction with *N*-methylisatin **1** and 4-hydroxy-6-methyl-2-pyrone **4**. The results listed in Table 3 show that good to excellent yields of coupling products were obtained under the optimized conditions using dimedone, 1,3-cyclopentanedione, 1,3-indanedione, and 1-oxaspiro[5.5]-undecane-2,4-dione as coupling partners (Table 3, entries 1−5). In addition, different 1,3-dicarbonyl reagents, a substituted hydroxypyrone, and 4-hydroxycoumarin were reacted with *N*-methylisatin **1** and 1,3-cyclohexanedione **2**. Cyclic sub-

(5) Numerous biologically active natural products contain the spirooxindole moiety. For selected recent examples in total synthesis, see: (a) Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6477. (b) Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6500. (c) Edmondson, S.; Danishefsky, S. J.; Sepp-Lorenzinol, L.; Rosen, N. *J. Am. Chem. Soc.* **1999**, *121*, 2147. (d) Alper, P. B.; Meyers, C.; Lerchner, A.; Siegel, D. R.; Carreira, E. M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3186. (e) Sebahar, P. R.; Williams, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 5666. (f) Onishi, T.; Sebahar, P. R.; Williams, R. M. *Org. Lett.* **2003**, *5*, 3135. (g) Onishi, T.; Sebahar, P. R.; Williams, R. M. *Tetrahedron* **2004**, *60*, 9503.

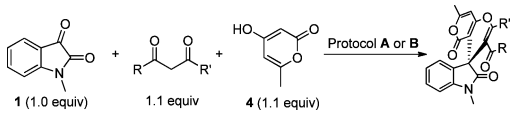
(6) See the Supporting Information for complete details.

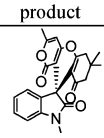
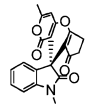
(7) For the synthesis of spirooxindoles via three-component reactions, see: (a) Zhu, S.; Ji, S.; Zhang, Y. *Tetrahedron* **2007**, *63*, 9365. (b) Elinson, M. N.; Ilovaisky, A. I.; Dorofeev, A. S.; Merkulova, V. M.; Stepanov, N. O.; Miloserdov, F. M.; Ogibin, Y. N.; Nikishin, G. I. *Tetrahedron* **2007**, *63*, 10543. (c) Jadidi, K.; Ghahremanzadeh, R.; Bazgir, A. *J. Comb. Chem.* **2009**, *11*, 341.

(8) Franz, A. K.; Dreyfuss, P. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 1020.

(9) We also examined a number of alternative solvents, however no improvement over $Cl(CH_2)_2Cl$ was observed.

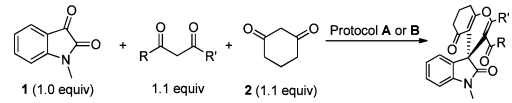
Table 3. Reaction of **4** with Different 1,3-Dicarbonyl Reagents

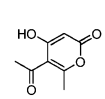
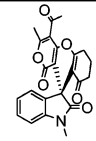
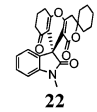
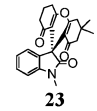
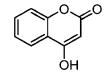
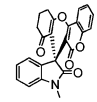
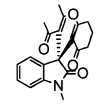


entry	1,3-dicarbonyl	product	protocol[a]	time	yield (%)[b]
1		 **16**	**A** **B**	12 h 80 min	93 93
2		 **17**	**A** **B**	16 h 80 min	71 70
3		 **18**	**A** **B**	12 h 80 min	60[c,d] 39[c,d]
4		 **19**	**A** **B**	16 h 80 min	68 65
5		 **20**	**A** **B**	16 h 80 min	70 41

[a] Protocol A: $SnCl_4$ (10 mol %), $Cl(CH_2)_2Cl$, 60 °C. Protocol B: $SnCl_4$•$5H_2O$ (10 mol %), $Cl(CH_2)_2Cl$, μW, 80 °C. [b] Isolated yields of compounds purified by chromatography on SiO_2. [c] 1,3-Indanedione (2.0 equiv). [d] See ref 10.

Table 4. Reaction of **2** with Different 1,3-Dicarbonyl Reagents



entry	1 3-dicarbonyl	product	protocol[a]	time	yield (%)[b]
1		 **21**	**A** **B**	16 h 80 min	75 70
2		 **22**	**A** **B**	16 h 80 min	60[c] 41[c]
3		 **23**	**A** **B**	16 h 80 min	51 47
4		 **24**	**A** **B**	16 h 80 min	63[d,e] 47[d,e]
5		 **25**	**A** **B**	48 h 4h	84[f] 65[f]
6		 **26**	**A** **B**	24 h 2.5 h	50[d,g] 32[d,g]

[a] Protocol A: $SnCl_4$ (10 mol %), $Cl(CH_2)_2Cl$, 60 °C. Protocol B: $SnCl_4$•$5H_2O$ (10 mol %), $Cl(CH_2)_2Cl$, μW, 80 °C. [b] Isolated yields of compounds purified by chromatography on SiO_2. [c] One and a half equivalents of each reagent was used. [d] Two equivalents of 1,3-dicarbonyl reagent was used. [e] See ref 10. [f] Solvent: $Cl(CH_2)_2Cl$/1,4-dioxane, 3:1; 2.5 equiv 4-hydroxycoumarin. [g] $Cu(OTf)_2$ (10 mol %) was used as catalyst.

strates afforded the desired spirooxindole products in moderate to good yields (Table 4, entries 1−5). However, reaction of 2,4-pentanedione catalyzed by $SnCl_4$ (10 mol %) did not result in formation of the desired product. When $Cu(OTf)_2$ (10 mol %) was used as catalyst, product **26** was obtained in 50% yield (Table 4, entry 6). The less reactive 4-hydroxycoumarin also gave a good yield of the three component coupling product (Table 4, entry 5). However, when 5,5-dimethyl-1,3-cyclohexanedione was reacted with *N*-methylisatin and 1,3-cyclohexanedione, the yield of the three-component product was low (Table 4, entry 3), due to increased production of the corresponding two-component reaction product.[6] The yield of the three-component product was diminished when the 1,3-dicarbonyl compounds are similar in pK_a.[11]

On the basis of these results, we propose two plausible pathways for the reaction (Scheme 2). *N*-Methylisatin **1** may coordinate with $SnCl_4$[8] and react with **2** to afford the aldol adduct **27**.[12] Dehydration of **27** by $SnCl_4$ affords indolenium intermediate **29**[13] which may be subsequently attacked by **4** to furnish **31** (path **A**).[14] Alternatively, the reaction may be initiated by aldol reaction of **4** with **1** to afford **28**, followed by dehydration and nucleophilic attack of **2**, to afford intermediate **31** (path **B**). Prior to addition of $SnCl_4$, mixing of **1**, **2**, and **4** provided an equilibrium mixture of **1**:**27**:**28** (5:3:2). In addition, in the absence of $SnCl_4$, mixing **1** and **2** affords a 1:1 equilibrium mixture (**1:27**) while mixing **1** and **4** affords only an 4:1 mixture (**1**:**28**).[6] The position of the complex equilibrium during the three-component reaction appears to be related to the pK_a of the corresponding dicarbonyl compounds such that the aldol adduct of the weaker carbon acid is favored, thereby biasing the reaction toward path A.[15] In combination with the enhanced nucleophilicity of the more acidic 1,3-dicarbonyl compound (*vide infra*), the three-component reaction pathway

(10) Under the reaction conditions, decomposition of 1,3-indanedione is competitive with the three-component coupling, presumably via self-condensation. The two-component product is not observed in appreciable quantities.

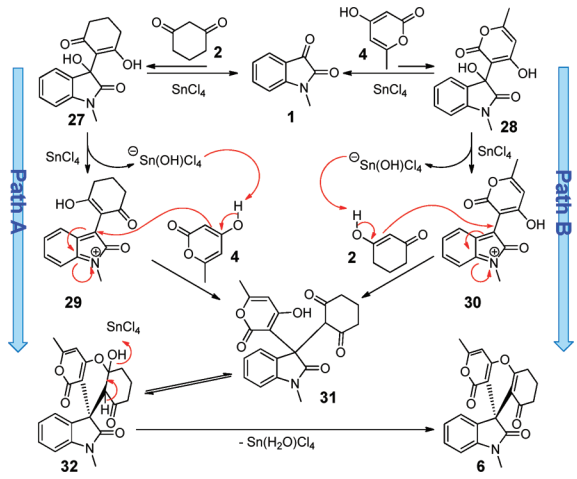
(11) We have characterized all byproducts for the reactions in Table 3 (entries 2 and 4), and Table 4 (entries 3 and 6). Two-component products of 1,3-diketones (such as **2**) are not observed, while the products incorporating two molecules of β-keto esters or hydroxypyrones were found as major byproducts. See the Supporting Information for further details.

(12) The structure of **7** was confirmed by X-ray analysis of the corresponding enol mesylate. See the Supporting Information for details.

(13) (a) England, D. B.; Merey, G.; Padwa, A. *Org. Lett.* **2007**, *9*, 3805. (b) England, D. B.; Merey, G.; Padwa, A. *Heterocycles* **2007**, *74*, 491.

(14) The product of $E1_{CB}$ elimination of **27** (an isatylidene) cannot be ruled out as a reaction intermediate. On the basis of non-bonding interactions and angle strain involved in such an intermediate, we currently favor a mechanism involving an indolenium intermediate.

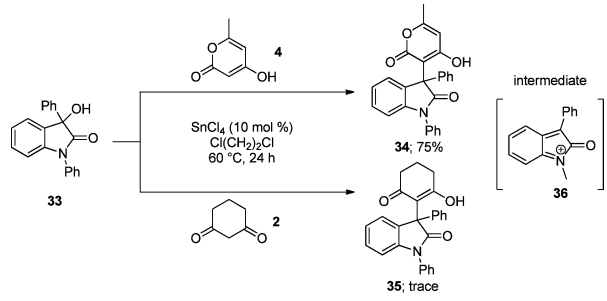
Scheme 2. Proposed Mechanism



thus predominates. Nucleophilic addition of the hydroxyl group of **31** to the adjacent carbonyl group, followed by dehydration catalyzed by $SnCl_4$, would provide the desired coupling product **6**.

To gain insight into the reaction pathways, we independently prepared two of the proposed intermediates along the mechanistic pathway. Intermediates **27** and **32** were independently prepared and converted to **6** under the three-component coupling conditions.[6] In addition, compound **33**, used as a model of **27**, was treated with **4** and **2** respectively under the three-component reaction conditions (Scheme 3). The products of this reaction

Scheme 3. Reactions via an Indolenium Intermediate



support the formation of indolenium intermediate **36** (similar to the proposed intermediate **29** in Scheme 2). The reaction of pyrone afforded the desired product **34** in good yield, while cyclohexandione afforded only trace amounts of **35**. These results suggest that hydroxypyrone **4** is a much better nucleophile for indolenium electrophiles such as **36** in comparison to **2**. By analogy, indolenium ions formed in our three-component reaction should react more quickly with **4** than **2**.

(15) The experimentally measured pKa of **2** in DMSO is 10.3 (15a),[15a] while the pK_a of **4** in 80% DMSO/H_2O is 6.83.[15b] (a) Arnett, E. M.; Harrelson, J. A. *J. Am. Chem. Soc.* **1987**, *109*, 809. (b) Tan, S.-F.; Ang, K.-P.; Jayachandran, H. *J. Chem. Soc., Perkin Trans. 2* **1983**, 472.

In addition, time course experiments indicate that intermediate **27** is formed as the primary product upon mixing **1**, **2**, and **4**.[6] Upon addition of $SnCl_4$, disappearance of **27** corresponds to the appearance of the three-component product **6**. On the basis of these results, in combination with the indolenium reactivity profile (Scheme 3), we propose that Path **A** (Scheme 2) is the major path for the formation of the three-component reaction products such as **6**. By monitoring the reaction using UPLC, kinetic profiles of the model reaction were obtained and clearly demonstrate the predominance of three-component product **6** compared to two-component products **3** and **5** throughout the reaction (Figure 1).

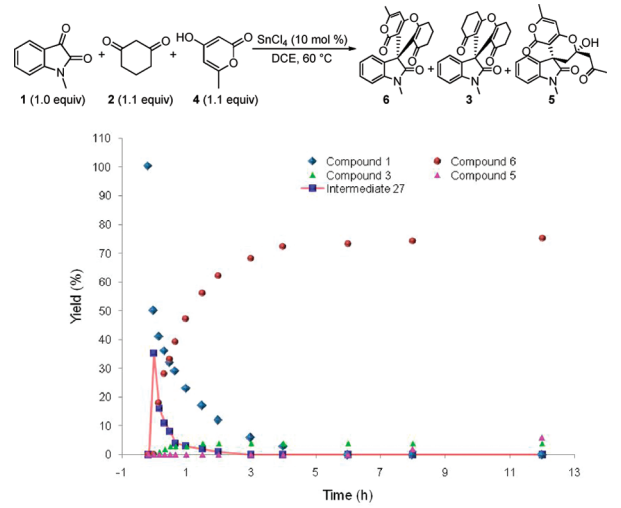


Figure 1. Kinetic plot of the three-component reaction. UPLC yields with biphenyl as internal standard (λ = 254 nm).

In summary, using a reaction screening approach we have identified the Lewis acid-catalyzed, three-component coupling of substituted isatins and two pK_a differentiated 1,3-dicarbonyls to synthesize various spirooxindoles bearing a pyranochromenedione ring system. Mechanistic studies indicate the likely involvement of an indolenium ion derived from the isatin and one 1,3-dicarbonyl component. Further studies to intercept this intermediate are currently underway and will be reported in due course.

Acknowledgment. Financial support from the NIGMS (P50-GM067041) and partial funding from Merck for a postdoctoral fellowship (S.K.) is gratefully acknowledged. NMR (CHE-0619339) and MS (CHE-0443618) facilities at Boston University are supported by the NSF. We thank Professor Aaron Beeler (Boston University) and Professor Scott Schaus (Boston University) for helpful discussions and Dr. Emil Lobkovsky (Cornell University) for X-ray crystallographic analysis.

Supporting Information Available: Experimental procedures and ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL902764K