ORGANIC LETTERS

XXXX
Vol. XX, No. XX
000–000

Metal-Free Oxidative Spirocyclization of Hydroxymethylacrylamide with 1,3-Dicarbonyl Compounds: A New Route to Spirooxindoles

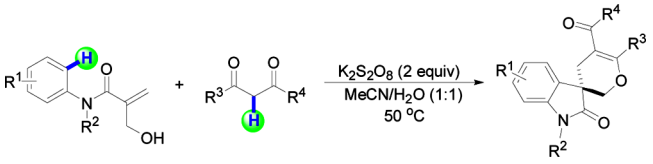
Hua Wang, Li-Na Guo,* and Xin-Hua Duan*

Department of Chemistry, School of Science and MOE Key Laboratory for Nonequilibrium Synthesis and Modulation of Condensed Matter, Xi'an Jiaotong University, Xi'an 710049, China

duanxh@mail.xjtu.edu.cn; guoln81@mail.xjtu.edu.cn

Received August 27, 2013

ABSTRACT



A metal-free oxidative spirocyclization of hydroxymethylacrylamide with 1,3-dicarbonyl compounds is described. The reaction proceeds through tandem dual C−H functionalization and intramolecular dehydration, in which two new C−C bonds and one C−O bond were formed. This method affords a novel and straightforward access to various spirooxindoles under mild conditions.

The heterocyclic spirooxindoles are of great interest in organic synthesis due to their highly potential biological activities as well as key precursors of natural alkaloids, and clinical pharmaceuticals.[1] Thus, numerous elegant synthetic approaches have been developed for the synthesis of structurally diverse spirooxindoles.[2] Among these methods, the azaspirooxindoles have been extensively investigated.[2] In contrast, less attention has been paid to the analogous oxaspirooxindoles. Recently, some efficient strategies such as multicomponent reactions,[3a−e] RCM,[3f] Prins cyclization,[3g,h] decarboxylative cyclization,[3i] and vinylogous aldol reactions[3j] to six-membered oxaspirooxindoles have been reported, but all the methods were limited to using the isatins and their derivatives as starting materials. Up to now, a tandem bicyclization process for the construction of six-membered oxaspirooxindoles has never been exploited and, thus, remains a challenging issue.

(1) For reviews, see: (a) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209. (b) Lin, H.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 36. (c) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748. For some recent examples, see: (d) Zhao, Y.; Liu, L.; Sun, W.; Lu, J.; McEachern, D.; Li, X.; Yu, S.; Bernard, D.; Ochsenbein, P.; Ferey, V.; Carry, J.-C.; Deschamps, J. R.; Sun, D.; Wang, S. *J. Am. Chem. Soc.* **2013**, *135*, 7223. (e) Zhao, Y.; Yu, S.; Sun, W.; Liu, L.; Lu, J.; McEachern, D.; Shargary, S.; Bernard, D.; Li, X.; Zhao, T.; Zou, P.; Sun, D.; Wang, S. *J. Med. Chem.* **2013**, *56*, 5553. (f) Bertamino, A.; Soprano, M.; Musella, S.; Rusciano, M. R.; Sala, M.; Vernieri, E.; Sarno, V. D.; Limatola, A.; Carotenuto, A.; Cosconati, S.; Grieco, P.; Novellino, E.; Illario, M.; Campiglia, P.; Gomez-Monterrey, I. *J. Med. Chem.* **2013**, *56*, 5407.

(2) For recent reviews, see: (a) Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, 3003. (b) Klein, J. E. M. N.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2011**, 6821. (c) Singh, G. S.; Desta, Z. Y. *Chem. Rev.* **2012**, *112*, 6104. (d) Rios, R. *Chem. Soc. Rev.* **2012**, *41*, 1060. (e) Dalpozzo, R.; Bartoli, G.; Bencivenni, G. *Chem. Soc. Rev.* **2012**, *41*, 7247. (f) Ball-Jones, N. R.; Badillo, J. J.; Franz, A. K. *Org. Biomol. Chem.* **2012**, *10*, 5165. (g) Hong, L.; Wang, R. *Adv. Synth. Catal.* **2013**, *355*, 1023.

(3) (a) Shanthi, G.; Subbulakshmi, G.; Perumal, P. T. *Tetrahedron* **2007**, *63*, 2057. (b) Zhu, S.-L.; Ji, S.-J.; Zhang, Y. *Tetrahedron* **2007**, *63*, 9365. (c) Jadidi, K.; Ghahremanzadeh, R.; Bazgir, A. *J. Comb. Chem.* **2009**, *11*, 341. (d) Li, Y.; Chen, H.; Shi, C.; Shi, D.; Ji, S. *J. Comb. Chem.* **2010**, *12*, 231. (e) Liang, B.; Kalidindi, S.; Porco, J. A., Jr.; Stephenson, C. R. J. *Org. Lett.* **2010**, *12*, 572. (f) Alcaide, B.; Almendros, P.; Rodríguez-Acebes, R. *J. Org. Chem.* **2006**, *71*, 2346. (g) Castaldi, M. P.; Troast, D. M.; Porco, J. A., Jr. *Org. Lett.* **2009**, *11*, 3362. (h) Wang, J.; Crane, E. A.; Scheidt, K. A. *Org. Lett.* **2011**, *13*, 3086. (i) Shintani, R.; Hayashi, S.-y.; Murakami, M.; Takeda, M.; Hayashi, T. *Org. Lett.* **2009**, *11*, 3754. (j) Babu, T. H.; Karthik, K.; Perumal, P. T. *Synlett* **2010**, 1128.

(4) (a) Jaegli, S.; Dufour, J.; Wei, H.-L.; Piou, T.; Duan, X.-H.; Vors, J.-P.; Neuville, L.; Zhu, J. *Org. Lett.* **2010**, *12*, 4498. (b) Wu, T.; Mu, X.; Liu, G. *Angew. Chem., Int. Ed.* **2011**, *50*, 12578. (c) Mu, X.; Wu, T.; Wang, H.-Y.; Guo, Y.-L.; Liu, G. *J. Am. Chem. Soc.* **2012**, *134*, 878. (d) Wei, W.-T.; Zhou, M.-B.; Fan, J.-H.; Liu, W.; Song, R.-J.; Liu, Y.; Hu, M.; Xie, P.; Li, J.-H. *Angew. Chem., Int. Ed.* **2013**, *52*, 3638. (e) Li, Y.-M.; Sun, M.; Wang, H.-L.; Tian, Q.-P.; Yang, S.-D. *Angew. Chem., Int. Ed.* **2013**, *52*, 3972. (f) Xie, J.; Xu, P.; Li, H.; Xue, Q.; Jin, H.; Cheng, Y.; Zhu, C. *Chem. Commun.* **2013**, *49*, 5672. (g) Wei, X.-H.; Li, Y.-M.; Zhou, A.-X.; Yang, T.-T.; Yang, S.-D. *Org. Lett.* **2013**, *15*, 4158.

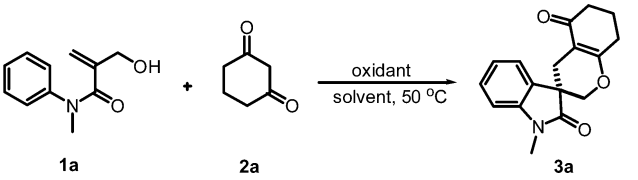
10.1021/ol402473m

The catalytic difunctionalization of acrylamides via direct C−H bond functionalization has attracted much attention in the past few years and has been applied successfully for the synthesis of various functionalized oxindoles.[2b,4] In particular, several metal-free oxidative coupling/cyclization reactions were also discovered.[5] Related elegant studies on radical cyclization strategies have been previously reported for spirooxindoles by Murphy and Curran.[6a−c] However, a tandem approach toward the more complex spirooxindoles employing acrylamides and its derivatives as a substrate with other reactants through direct C−H bond functionalization has scarcely been investigated.[4a,6] As part of our continued interest in the difunctionalization of acrylamides,[7] we herein report the metal-free oxidative spirocyclization of hydroxymethylacrylamide with 1,3-dicarbonyl compounds, providing an efficient route to more valuable oxaspirooxindoles.[8] This new general approach allows the formation of two C−C bonds and one C−O bond in one synthetic step (Table 1).

In our initial studies, 2-hydroxymethyl-*N*-methyl-*N*-phenylacrylamide (**1a**) was treated with 1,3-cyclohexanedione (**2a**) in the presence of 1 equiv of $K_2S_2O_8$ in CH_2Cl_2/H_2O (1:1) at 50 °C (Table 1, entry 1).[7b] Gratifyingly, the desired spirooxindole **3a** was obtained in 28% yield. Among the solvents tested, CH_3CN/H_2O (1:1) was found to be the best one (entry 5). Further screening of oxidants revealed that $K_2S_2O_8$ is better than $(NH_4)_2S_2O_8$ (entry 6), whereas other oxidants gave none of the desired product (entries 7 and 8). We were pleased to find that increasing the amount of $K_2S_2O_8$ up to 2 equiv improved the yield from 70% to 90% (entry 9). It should be noted that **3a** was isolated in low yield in the absence of water (entry 10), whereas addition of 18-crown-6 afforded a satisfying result (entry 11).

To explore the scope of the reaction, various hydroxymethylacrylamides **1** were first examined under the optimized reaction conditions (Scheme 1). As shown in Scheme 1, a range of acrylamides having different substituents on the aniline moieties underwent the desired transformation smoothly to give the spirooxindoles **3b**−**i** in good to high yields. It is worth noting that the reaction is tolerant of many functional groups such as iodo, cyano, and ester (**3e**−**g**). The *ortho*-methyl and fluoro substituted substrates were also effective; therefore treatment of **1h** and **1i** with **2a** afforded the corresponding products **3h** and **3i** in 78% and 94% yields, respectively. For 2-hydroxymethyl-*N*-methyl-*N*-naphthylacrylamide **1j**, the desired product **3j** was also formed albeit in low yield. Finally, changing the protecting group on the *N* tether from the methyl group to benzyl also gave the desired product **3k** in 60% yield. Unfortunately, we have not found a suitable method to prepare the unprotected hydroxymethylacrylamide at

Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a

entry	oxidant (equiv)	solvent	yield (%)[b]
1	$K_2S_2O_8$ (1)	CH_2Cl_2/H_2O (1:1)	28
2	$K_2S_2O_8$ (1)	EtOAc/H_2O (1:1)	62
3	$K_2S_2O_8$ (1)	DMF/H_2O (1:1)	32
4	$K_2S_2O_8$ (1)	H_2O	64 (86)[c]
5	$K_2S_2O_8$ (1)	CH_3CN/H_2O (1:1)	70
6	$(NH_4)_2S_2O_8$ (1)	CH_3CN/H_2O (1:1)	61
7	oxone (1)	CH_3CN/H_2O (1:1)	n.r.[d]
8	BQ (1)	CH_3CN/H_2O (1:1)	n.r.[d]
9	$K_2S_2O_8$ (2)	CH_3CN/H_2O (1:1)	90
10	$K_2S_2O_8$ (2)	CH_3CN	14
11	$K_2S_2O_8$ (2)	CH_3CN	64[e]

[a] Reaction conditions: **1a** (0.2 mmol, 1 equiv), **2a** (0.4 mmol, 2 equiv), solvent (1 mL), oxidant (1 equiv), 50 °C, 28 h. [b] Yield of isolated product. [c] The yield in parentheses using 2 equiv of $K_2S_2O_8$. [d] n.r. = no reaction. [e] 2 equiv of 18-crown-6 were added.

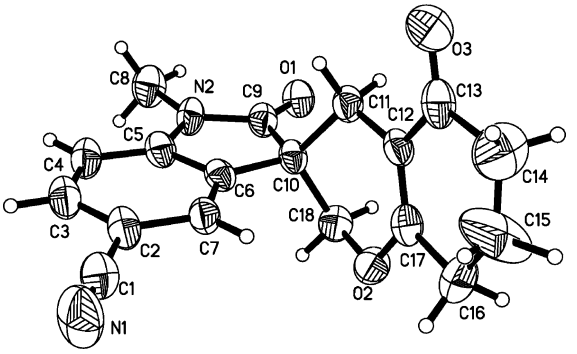


Figure 1. X-ray crystal structure of the spirooxindole **3f**.

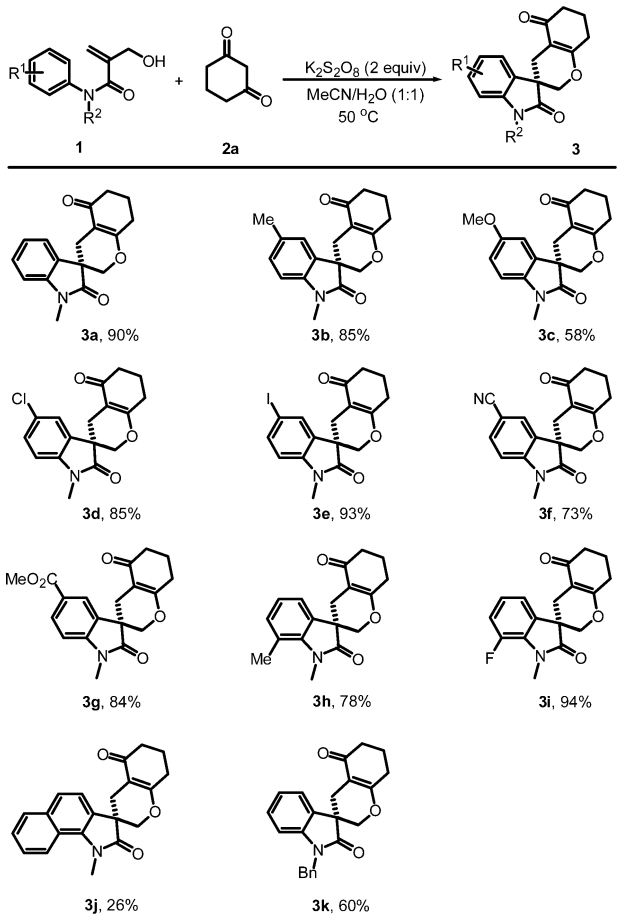
(5) (a) Wu, T.; Zhang, H.; Liu, G. *Tetrahedron* **2012**, *68*, 5229. (b) Zhou, M.-B.; Song, R.-J.; Ouyang, X.-H.; Liu, Y.; Wei, W.-T.; Deng, G.-B.; Li, J.-H. *Chem. Sci.* **2013**, *4*, 2690. (c) Li, X.; Xu, X.; Hu, P.; Xiao, X.; Zhou, C. *J. Org. Chem.* **2013**, *78*, 7343. (d) Matcha, K.; Narayan, R.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2013**, *52*, 7985.

(6) (a) Lizos, D. E.; Murphy, J. A. *Org. Biomol. Chem.* **2003**, *1*, 117. (b) González-López de Turiso, F.; Curran, D. P. *Org. Lett.* **2005**, *7*, 151. (c) Ueda, M.; Uenoyama, Y.; Terasoma, N.; Doi, S.; Kobayashi, S.; Ryu, I.; Murphy, J. A. *Beilstein J. Org. Chem.* **2013**, *9*, 1340. For the palladium-catalyzed domino process leading to spirooxindoles through *ortho*-halo substituted anilide cyclization, see: (d) Ashimori, A.; Overman, L. E. *J. Org. Chem.* **1992**, *57*, 4571. (e) D'Souza, D. M.; Rominger, F.; Müller, T. J. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 153. (f) Ruck, R. T.; Huffman, M. A.; Kim, M. M.; Shevlin, M.; Kandur, W. V.; Davies, I. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 4711. (g) Jaegli, S.; Erb, W.; Retailleau, P.; Vors, J.-P.; Neuville, L.; Zhu, J. *Chem.—Eur. J.* **2010**, *16*, 5863. (h) Piou, T.; Neuville, L.; Zhu, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 11561. For the metal-free oxidative domino process leading to spirooxindoles through anilide cyclization, see: (i) Wang, J.; Yuan, Y.; Xiong, R.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. *Org. Lett.* **2012**, *14*, 2210.

(7) (a) Meng, Y.; Guo, L.-N.; Wang, H.; Duan, X.-H. *Chem. Commun.* **2013**, *49*, 7540. (b) Wang, H.; Guo, L.-N.; Duan, X.-H. *Adv. Synth. Catal.* **2013**, *355*, 2222. (c) Zhou, S.-L.; Guo, L.-N.; Wang, H.; Duan, X.-H. *Chem.—Eur. J.* **2013**, *19*, 12970.

(8) Jiang, X.; Sun, Y.; Yao, J.; Cao, Y.; Kai, M.; He, N.; Zhang, X.; Wang, Y.; Wang, R. *Adv. Synth. Catal.* **2012**, *354*, 917.

Scheme 1. Scope of Hydroxymethylacrylamides[a]



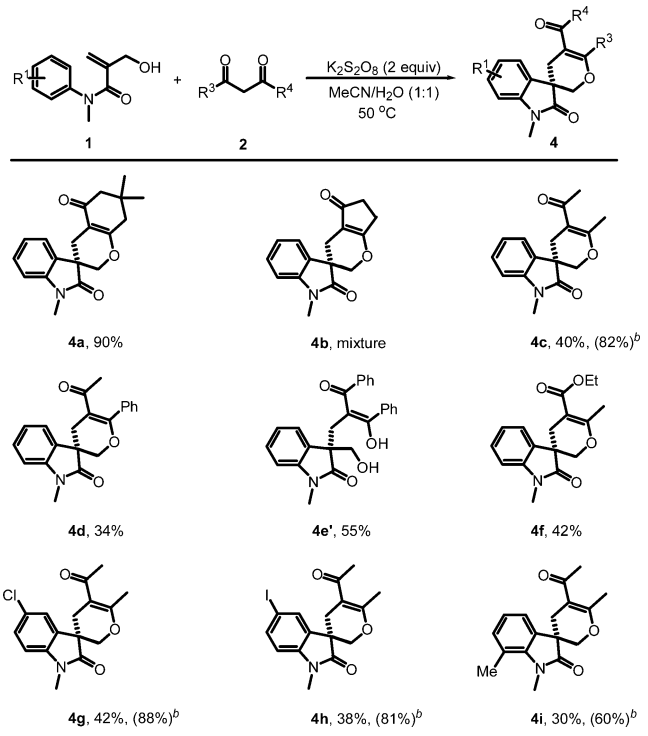
[a] Reaction conditions: **1** (0.2 mmol, 1 equiv), **2a** (0.4 mmol, 2 equiv), MeCN/H_2O (1:1, 1 mL), $K_2S_2O_8$ (2 equiv), 50 °C, 28 h.

present. The structure of **3f** was further unambiguously confirmed by X-ray diffraction analysis (Figure 1).[9]

Next, the reactivities of different 1,3-dicarbonyl compounds were investigated (Scheme 2). In addition to cyclic β-diketone **2a**, 5,5-dimethylcyclohexane-1,3-dione was also a satisfying substrate for this transformation (**4a**). Surprisingly, when 1,3-cyclopentanedione was used instead of 1,3-cyclohexanedione under the standard conditions, the desired product **4b** was obtained in less than 5% yield in addition to unidentified products; and most of the acrylamide remained unreacted. It is important to note that the phenyl group at the α-position of 1,3-dicarbonyl compound strongly affected the efficiency of the spirocyclization reaction. Benzoylacetone **2d** containing one phenyl group gave the desired spirooxindole product **4d** in 34% yield with high regioselectivity. Dibenzoylmethane **2e** bearing two phenyl groups led to the termination of the bicyclization process, affording the oxindole **4e′** in 55% isolated yield. This result suggested that the hydroxymethyl substituted oxindole might be the key intermediate

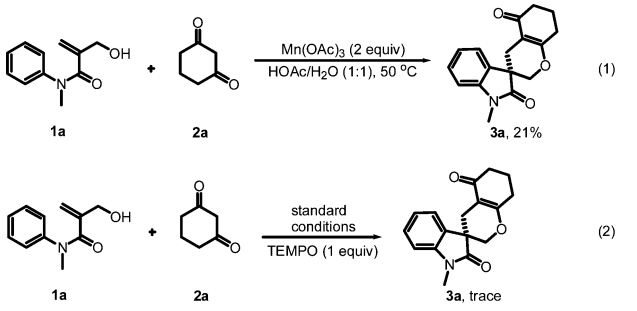
(9) Crystallographic data for spirooxindole **3f** have been deposited at the Cambridge Crystallographic Date Centre (CCDC 953997).

Scheme 2. Scope of 1,3-Dicarbonyl Compounds[a,b]



[a] Reaction conditions: **1** (0.2 mmol, 1 equiv), **2** (0.4 mmol, 2 equiv), MeCN/H_2O (1:1, 1 mL), $K_2S_2O_8$ (2 equiv), 50 °C, 28 h. [b] The numbers in parentheses are isolated yields for reactions performed in the presence of 10 mol % of $AgNO_3$ and 2 equiv of $K_2S_2O_8$.

in this tandem reaction (for details, see mechanism). Ethyl acetoacetate was less effective, resulting in a 42% yield (**4f**). Finally, hydroxymethylacrylamides having different groups reacted with 2,4-pentanedione, producing the desired

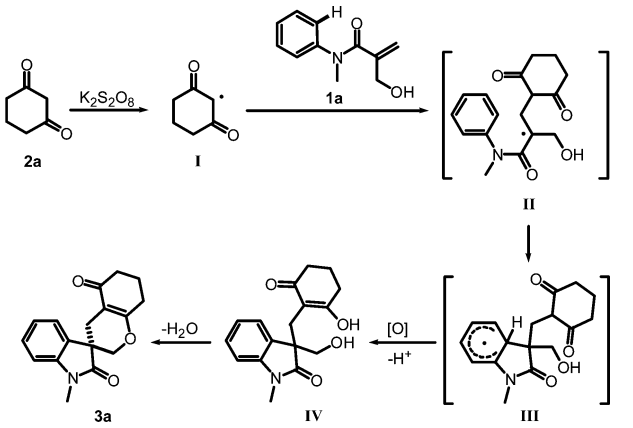


spirooxindoles **4c**, **4g**–**i** in 40%, 42%, 38%, and 30% yield, respectively, due to low conversion. To our delight, addition of 10 mol % $AgNO_3$ provided cleaner reactions and led to better yields when 2,4-pentanedione was used as the substrate (**4c**, **4g**–**i**). We presumed that the catalyst is beneficial for the formation of the hydroxyl-containing oxindoles, which are the key precursor of the spirooxindoles.

(10) For reviews on the Mn(III)-mediated free-radical cyclization reactions of 1,3-dicarbonyl compounds, see: (a) Iqbal, J.; Bhatia, B.; Nayyar, N. K. *Chem. Rev.* **1994**, *94*, 519. (b) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339.

(11) See Supporting Information for details.

Scheme 3. Proposed Mechanism



A Mn(III)-mediated oxidative free radical cyclization reaction of 1,3-dicarbonyl compounds and alkenes has previously been described in the literature.[10] Thus, the reaction of **1a** and **2a** was conducted with stoichiometric $Mn(OAc)_3$ in $HOAc/H_2O$, but afforded only a 21% yield of **3a** (eq 1).[11] Furthermore, the reaction was also suppressed when TEMPO, a radical-trapping reagent, was added (eq 2). Thus, we speculated that the reaction proceeded through free-radical substitution, which was consistent with the mechanisms proposed in previous reports.[4d−g,5,7] A possible mechanism for the reaction of hydroxymethylacrylamide **1a** with 1,3-cyclohexanedione **2a** is depicted in Scheme 3. The deprotonation of **2a** gives radical **I** in the presence of $K_2S_2O_8$, which then adds to **1a** to afford radical **II**. The radical **II** undergoes an intramolecular cyclization to generate radical **III**,[4d−g,5] followed by oxidation of **III** into the corresponding carbocation, which loses H^+ to produce the annulated oxindole **IV**.[7b] Finally, intermediate **IV** undergoes an intramolecular dehydration to afford spirooxindole **3a**.

In summary, we have developed a metal-free oxidative spirocyclization of hydroxymethylacrylamide with 1,3-dicarbonyl compounds via tandem sp^3 C−H and sp^2 C−H functionalization followed by intramolecular dehydration. The process exhibits significant functional group tolerance and atom economy and allows the synthesis of structurally diverse functionalized spirooxindoles under mild conditions. These simple and environmentally benign processes would extend the potential application of valuable spirooxindole derivatives in synthetic and medicinal chemistry.

Acknowledgment. Financial support from the National Natural Science Foundation of China (Nos. 21102111, 21102110) and the Fundamental Research Funds of the Central Universities is greatly appreciated.

Supporting Information Available. Experimental procedures and spectroscopic data of new compounds. X-ray data for **3f**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.