Tetrahedron Letters 51 (2010) 5473–5475

Contents lists available at ScienceDirect

Tetrahedron Letters

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

A new stereoselective approach for the synthesis of substituted 3-cyclopropylmethylene-1,3-dihydro-indol-2-one via the condensation reaction of *cis*-1-aryl-2-benzoyl-3,3-dicyanocyclopropanes with oxindole in water

Dong Zhou [a,†], Haigang Yu [a,†], Ying Liu [a], Jie Chen [a], Hongmei Deng [c], Min Shao [c], Zhongjiao Ren [a,*], Weiguo Cao [a,b,*]

[a] Department of Chemistry, Shanghai University, Shanghai 200444, China
[b] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Shanghai 200032, China
[c] Instrumental Analysis and Research Center, Shanghai University, Shanghai 200444, China

ARTICLE INFO

Article history:
Received 7 April 2010
Revised 2 August 2010
Accepted 10 August 2010
Available online 13 August 2010

Keywords:
Vinylcyclopropane
Cyclopropyl ketone
Water
Oxindole
Stereoselective synthesis

ABSTRACT

A new stereoselective approach for the synthesis of substituted 3-cyclopropylmethylene-1,3-dihydro-indol-2-one via the condensation reaction of *cis*-1-aryl-2-benzoyl-3,3-dicyanocyclopropanes with oxindole in water was achieved.

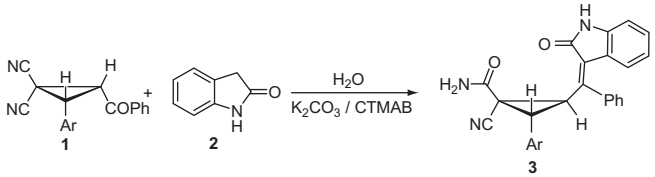
Vinylcyclopropanes occupy a central position in cyclopropane chemistry due to their occurrence in numerous natural products,[1] wide range of biological activities,[2] and utility as versatile intermediates for synthesis of natural and non-natural products.[3] Therefore, there has been growing interest in developing efficient methods for synthesis of vinylcyclopropane. A number of synthetic approaches to these compounds have been reported in recent years.[4]

Knoevenagel condensation of carbonyl compounds with active methylene components is an important method for the formation of carbon–carbon double bond. Cyclopropyl ketones have been shown to be useful synthetic substrates in organic synthesis.[5] To the best of our knowledge, the synthesis of vinylcyclopropane from cyclopropyl ketone and active methylene compounds has rarely been reported. Thus, we decided to explore this condensation reaction and provided an efficient approach for the preparation of vinylcyclopropanes.

In recent years, the concept of privileged structures, which repeated occurrence in biologically active molecules become important for the design and synthesis of drug candidates. The indole framework is a versatile and important structural motif frequently found in natural products, pharmaceuticals, and other synthetic compounds.[6]

As a result, the development of new method for synthesis of functionalized indoles has been the focus for many decades and continues to be an active and rewarding research area.[7] Based on the facts mentioned above, we hope to stereoselectively construct the cyclopropylmethylene-indoles in order to test their biological and pharmaceutical activities and explore their synthetic utility as versatile precursors for construction of complex indoles.

The development of reactions in water is one of the most important topics in current chemistry, because water is the most abun-



Scheme 1. Synthesis of 3-cyclopropylmethylene-1,3-dihydro-indol-2-one.

* Corresponding authors. Tel./fax: +86 21 66134856.
E-mail addresses: zjren@shu.edu.cn (Z. Ren), wgcao@staff.shu.edu.cn (W. Cao).
† With equal contribution to this work.

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.08.025

Table 1
Optimization of condition for condensation in water

Entry	Surfactant	base	Time (h)	Temp (°C)	Yield%
1	None	K_2CO_3	24	50	30
2	TBAB	K_2CO_3	12	50	60
3	TBAI	K_2CO_3	12	50	52
4	BDMTAC	K_2CO_3	12	50	72
5	BTEAC	K_2CO_3	12	50	64
6	CTMAB	K_2CO_3	12	50	85
7	CTMAB	$NaHCO_3$	12	50	69
8	CTMAB	$KF{\cdot}2H_2O$	12	50	62
9	CTMAB	K_2CO_3	12	25	70
10	CTMAB	K_2CO_3	12	40	76
11	CTMAB	K_2CO_3	12	60	69

TBAB: tetrabutylammonium bromide; TBAI: tetrabutylammonium iodide; BDMTAC: benzyldimethyltetradecylammonium chloride; BTEAC: benzyltriethylammonium chloride; CTMAB: cetyltrimethylammonium bromide.

Table 2
Synthesis of **3a–i** from cyclopropyl ketone and oxindole[a]

Product	Ar	Reaction time (h)	Yield[b] (%)
3a	4-ClC_6H_4	16	85
3b	2-ClC_6H_4	22	77
3c	4-$NO_2C_6H_4$	12	80
3d	4-FC_6H_4	18	79
3e	C_6H_5	20	81
3f	4-$CH_3C_6H_4$	25	83
3g	4-$CH_3OC_6H_4$	36	78
3h	2,4-$(CH_3)_2C_6H_3$	30	80
3i	2,4-$(CH_3O)_2C_6H_3$	48	75

[a] Typical reaction condition: a mixture of cyclopropane **1** (1 equiv), oxindole **2** (1.1 equiv), K_2CO_3 (3 equiv), and CTMAB (0.1 equiv) in water (5 mL) was stirred at 50 °C.
[b] Isolated yield by silica gel chromatography.

dant, environmentally benign, and cheapest solvent. In addition, some reactions in water have brought surprising and unforeseen results.[8] With these considerations in mind, we now report a new approach for stereoselective synthesis of substituted 3-cyclopropylmethylene-1,3-dihydro-indol-2-one via the condensation reaction of *cis*-1-aryl-2-benzoyl-3,3-dicyanocyclopropanes[9] with oxindole in water (Scheme 1).

The surfactant played an important role in solving the problem of solubility of organic compounds in water. Our initial studies started with the screening of a suitable surfactant. In the model experiment, the mixture of cyclopropane **1a** (1 equiv), oxindole **2** (1.1 equiv), K_2CO_3 (3 equiv), and surfactant (0.1 equiv) in water (5 mL) was stirred at 50 °C. The results were shown in Table 1. Cetyltrimethylammonium bromide (CTMAB) was the most effective among these surfactants (Table 1, entry 6). Whereas **3a** was obtained in 30% in the absence of surfactant (Table 1, entry 1), so this result indicated that the surfactant in this reaction was indispensable. Then, the bases and reaction temperature were examined. The best base is K_2CO_3 and temperature is 50 °C for this reaction.

To investigate the generality of this process, the reactions of various cyclopropanes with oxindole were performed at 50 °C in water in the presence of K_2CO_3. As shown in Table 2, this reaction proceeded smoothly to give corresponding products **3a–i** in 75–85% yields. The structures of **3a–i** were confirmed by MS, IR, ^1H NMR, ^{13}C NMR, and microanalysis. Further confirmation of the configuration was verified by X-ray diffraction of compound **3a** (Fig. 1).[10]

A plausible mechanism for the formation of 3-cyclopropylmethylene-1,3-dihydro-indol-2-one is shown in Scheme 2. First, the inversion of cyclopropane **1** occurred in aqueous solution in the presence of K_2CO_3 to form the *trans* isomer **A**, which has been proved by stirring **1a** in aqueous solution in the presence of

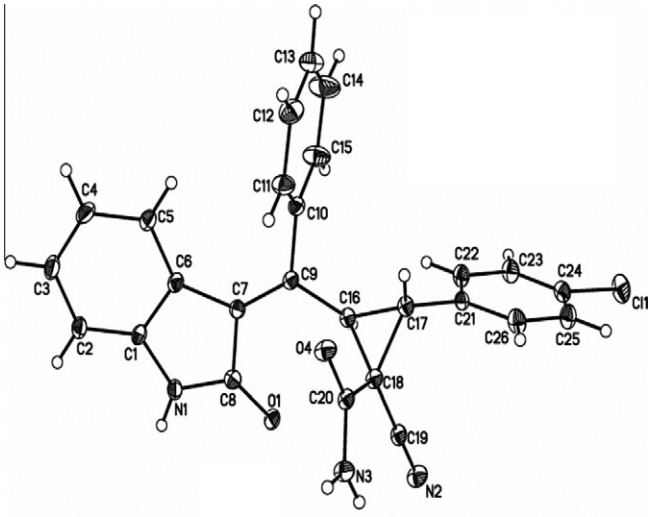
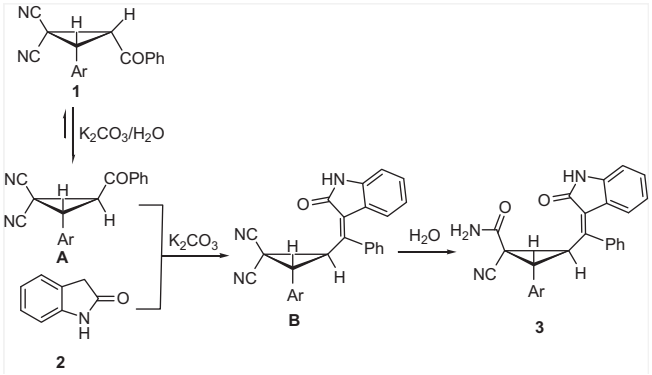


Figure 1. X-ray crystal structure of **3a**.



Scheme 2. Mechanism for construction of 3-cyclopropylmethylene-1,3-dihydro-indol-2-one.

K_2CO_3 and surfactant. Next, Knoevenagel condensation of carbonyl group of **A** with active methylene moiety of oxindole **2** yielded compound **B**. Finally, hydrolysis of cyano group took place to get product **3**.

In conclusion, we developed a new stereoselective approach for the synthesis of substituted 3-cyclopropylmethylene-1,3-dihydro-indol-2-one via the condensation reaction of *cis*-1-aryl-benzoyl-3,3-dicyanocyclopropanes with oxindole in water.

Acknowledgments

Thanks are due to the National Natural Science Foundation of China (Grant No. 20872088) and the Leading Academic Discipline Project of Shanghai Municipal Education Commission (Grant No. J50102) for their financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.08.025.

References and notes

1. (a) Wenssjohann, L. A.; Brandt, W.; Thiemann, T. *Chem. Rev.* **2003**, *103*, 1625; (b) Lanmarre, D.; Anderson, P. C.; Bailey, M.; Beaulieu, P.; Bolger, G.; Bonneau, P.; Boes, M.; Cameron, D. R.; Cartier, M.; Cordingley, M. G.; Faucher, A.-M.; Goudreau, N.; Kawai, S. H.; Kukolj, G.; Lagace, L.; LaPlante, S. R.; Narjes, H.; Poupart, M.-A.; Rancourt, J.; Sentjens, R. E.; St. George, R.; Simoneau, B.;

Steinmann, G.; Thibeault, D.; Tsantrizos, Y. S.; Weldon, S. M.; Yong, C.-L.; Llins-Brunet, M. *Nature* **2003**, *426*, 186.
2. (a) Yoshida, M.; Ezali, M.; Hashimoto, M.; Yamashita, M.; Shigematsu, N.; Okuhara, M.; Horikoshi, K. *J. Antibiot.* **1990**, *18*, 748; (b) Rancourt, J.; Cameron, D. R.; Gorys, V.; Lamarre, D.; Poirier, M.; Thibeault, D.; Llins-Brunet, M. *J. Med. Chem.* **2004**, *47*, 6584.
3. (a) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudicky, T. *Chem. Rev.* **1989**, *89*, 165; (b) Barrett, A. G. M.; Tam, W. *J. Org. Chem.* **1997**, *62*, 7673; (c) Trost, B. M.; Toste, F. D.; Shen, H. *J. Am. Chem. Soc.* **2000**, *122*, 2379; (d) Patra, P. K.; Reissig, H.-U. *Synlett* **2001**, 33; (e) Zuo, G.; Louie, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 2277; (f) Sebelius, S.; Olsson, V. J.; Szab?, K. J. *J. Am. Chem. Soc.* **2005**, *127*, 10478; (g) Wender, P. A.; Haustedt, L. O.; Lim, J.; Love, J. A.; Williams, T. J.; Yoon, J. *J. Am. Chem. Soc.* **2006**, *128*, 6302.
4. (a) Aqil, R.; Motherwell, W. B.; Roberts, L. R.; Russell, C. A. *Tetrahedron Lett.* **2002**, *43*, 9671; (b) Ma, S.; Jiao, N.; Yang, Q.; Zheng, Z. *J. Org. Chem.* **2004**, *69*, 6463; (c) Jiang, H.; Deng, X.; Sun, X.; Tang, Y.; Dai, L.-X. *J. Org. Chem.* **2005**, *70*, 10202; (d) Murelli, R. P.; Cataln, S.; Gannon, M. P.; Snapper, M. L. *Tetrahedron Lett.* **2008**, *49*, 5714.
5. (a) Bertozzi, F.; Gustafsson, M.; Olsson, R. *Org. Lett.* **2002**, *4*, 3147; (b) Yang, Y.-H.; Shi, M. *J. Org. Chem.* **2005**, *70*, 10082; (c) Wurz, R. P.; Charette, A. B. *Org. Lett.* **2005**, *7*, 2313; (d) Liu, L.; Montgomery, J. *J. Am. Chem. Soc.* **2006**, *128*, 5348.
6. (a) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th ed.; Blackwell Science: Oxford, 2000; (b) Sundberg, R. J. *Indoles*; Academic Press: London, 1996; (c) Agarwal, S.; Caemmerer, S.; Filali, S.; Froehner, W.; Knoell, J.; Krahl, M. P.; Reddy, K. R.; Knolker, H.-J. *Curr. Org. Chem.* **2005**, *9*, 1601; (d) O'Connor, S. E.; Maresh, J. *J. Nat. Prod. Rep.* **2006**, *23*, 532.
7. (a) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172; (b) Bandini, M.; Melloni, R.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550; (c) Jensen, K. B.; Thorhange, J.; Hazel, R. G.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 160; (d) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 287.
8. (a) Grieco, P. A. *Organic Synthesis in Water*; Blackie Academic and Professional: London, 1988; (b) Li, C.-J.; Chan, T. H. *Organic Reactions in Aqueous Media*; John Wiley and Sons: New York, 1997; (c)*Organic Reaction in Water*; Lindstrom, U. M., Ed.; Blackwell Publishing: Oxford, 2007; (d) Lindström, U. M. *Chem. Rev.* **2002**, *102*, 2751; (e) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095; (f) Pirrung, M. C.; Sarma, K. D. *J. Am. Chem. Soc.* **2004**, *126*, 444.
9. Ren, Z.; Cao, W.; Ding, W.; Wang, Y. *Synthesis* **2005**, *35*, 2718.
10. CCDC-748160 (**3a**) contains all crystallographic details of this publication and is available free of charge at http://www.ccdc.cam.ac.uk/consts/retrieving.html or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, GB-Cambridge CB21EZ; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk.
Unit cell parameters: *a*: 10.5677 Å; *b*: 12.2458 Å; *c*: 12.458(8) Å; alpha: 93.359; beta: 107.423; gamma: 100.958; space group: $P\bar{1}$.