ORGANIC LETTERS

2012
Vol. 14, No. 20
5172–5175

Facile Synthesis of Dispirooxindole-Fused Heterocycles via Domino 1,4-Dipolar Addition and Diels–Alder Reaction of in Situ Generated Huisgen 1,4-Dipoles

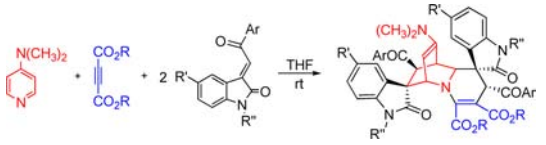
Jing Sun, Yan Sun, Hui Gong, Ya-Jing Xie, and Chao-Guo Yan*

College of Chemistry & Chemical Engineering, Yangzhou University, Yangzhou 225002, China

cgyan@yzu.edu.cn

Received July 12, 2012

ABSTRACT



A facile synthetic protocol was developed for the efficient synthesis of complex dispirooxindole-fused heterocycles via a three-component reaction. The key strategies involve a domino 1,4-dipolar addition and Diels–Alder reaction of the in situ generated Huisgen 1,4-dipoles from the addition reaction of 4-dimethylaminopyridine with acetylenedicarboxylate to 3-phenacylideneoxindole.

Multicomponent reactions have received considerable attention because of their wide range of applications in organic and medical chemistry for the creation of structural diversity and combinatorial libraries.[1,2] Multicomponent reactions are extremely convergent, producing a remarkable increase in molecular complexity in one step. In recent years, the use of multicomponent reactions has emerged as a powerful and efficient tool for the synthesis of structurally diverse molecules, and many recently designed multicomponent reactions have been reported.[3,4] The diverse reactivity of Huisgen 1,4-dipoles, which are easily generated from the addition of nitrogen heterocycles or amines to electron-deficient alkynes, has been widely used in multicomponent reactions, leading to a number of carbon–carbon bond formation reactions and heterocyclic constructions.[5–11] In this study, we wish to report the

(1) (a) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123–131. (b) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89.

(2) (a) Zhu, J.; Bienayme, H. *Multicomponent Reactions*; Wiley: Weinheim, 2005. (b) D'Souza, D. M.; Muller, T. J. *J. Chem. Soc. Rev.* **2007**, *36*, 1095–1108. (c) Tietze, L. F.; Kinzel, T.; Brazel, C. C. *Acc. Chem. Res.* **2009**, *42*, 367–378.

(3) (a) Touré, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439–4486. (b) Candeias, N. R.; Montalbano, F.; Cal, P. M.; Gois, P. M. P. *Chem. Rev.* **2010**, *110*, 6169–6193.

(4) (a) Sunderhaus, J. D.; Dockendorff, C.; Martin, S. F. *Tetrahedron* **2009**, *65*, 6454–6469. (b) Bonne, D.; Coquerel, Y.; Constantieux, T.; Rodriguez, J. *Tetrahedron: Asymmetry* **2010**, *21*, 1085–1109. (c) Wang, K.; Nguyen, K.; Huang, Y. J.; Dömling *J. Comb. Chem.* **2009**, *11*, 920–927.

(5) (a) Huisgen, R. *Topics in Heterocyclic Chemistry*; Castle, R., Ed.; John Wiley and Sons: New York, NY, 1969; Chapter 8, p 223. (b) Huisgen, R.; Morikawa, M.; Herbig, K.; Brunn, E. *Chem. Ber.* **1967**, *100*, 1094–1106.

(6) (a) Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekanth, A. R.; Mathen, J. S.; Balagopal, L. *Acc. Chem. Res.* **2003**, *36*, 899–907. (b) Nair, V.; Menon, R. S.; Sreekanth, A.; Abhilash, N.; Biju, A. T. *Acc. Chem. Res.* **2006**, *39*, 520–530.

(7) (a) Liu, W. B.; Jiang, H. F.; Huang, L. B. *Org. Lett.* **2010**, *12*, 312–315. (b) Shen, Y. X.; Jiang, H. F.; Chen, Z. W. *J. Org. Chem.* **2010**, *75*, 1321–1324. (c) Liu, W. B.; Jiang, H. F.; Zhang, M.; Qi, C. R. *J. Org. Chem.* **2010**, *75*, 966–968.

(8) (a) Yavari, I.; Mirzaei, A.; Moradi, L.; Khalili, G. *Tetrahedron Lett.* **2010**, *51*, 396–398. (b) Yavari, I.; Seyfi, S.; Hossaini, Z. *Tetrahedron Lett.* **2010**, *51*, 2193–21949.

(9) (a) Alizadeh, A. A.; Rostamnia, S.; Zhu, L. G. *Tetrahedron Lett.* **2010**, *51*, 4750–4754. (b) Teimouri, M. B.; Abbasi, T. *Tetrahedron* **2010**, *66*, 3795–3800.

(10) (a) Sun, J.; Xia, E. Y.; Wu, Q.; Yan, C. G. *Org. Lett.* **2010**, *12*, 3678–3681. (b) Sun, J.; Sun, Y.; Xia, E. Y.; Yan., C. G. *ACS Comb. Sci.* **2011**, *13*, 436–441. (c) Sun, J.; Sun, Y.; Gao, H.; Yan, C. G. *Eur. J. Org. Chem.* **2011**, 6952–6956.

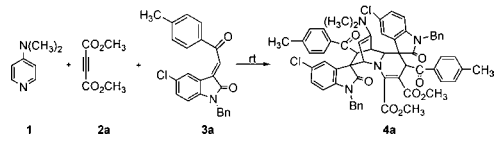
(11) (a) Yadav, J. S.; Reddy, B. V. S.; Rao, K. V. R.; Narender, R. *Tetrahedron Lett.* **2009**, *50*, 3963–3965. (b) Reddy, B. V. S.; Reddy, M. R.; Narasimhulu, G.; Yadav, J. S. *Tetrahedron Lett.* **2010**, *51*, 5677–5679.

10.1021/ol302530m
Published on Web 10/10/2012

efficient synthesis of novel dispirooxindole-fused heterocycles via domino three-component reactions of 4-dimethylaminopyridine (DMAP), acetylenedicarboxylates, and 3-phenacylideneoxindoles.

It is known that the domino reactions of isatin derivatives with Huisgen 1,4-dipoles formed in situ from pyridine, isoquinoline, and acetylenic esters can be used for constructing versatile spirooxindole systems.[12−14] Spirooxindoles are one of the most important classes of naturally occurring substances, characterized by highly pronounced biological properties; these molecules are also the core structure of many synthetic pharmaceuticals.[15−17] Thus, we decided to investigate the domino reactions of Huisgen 1,4-dipoles with 3-phenacylideneoxindoles. An equimolar mixture of 4-dimethylaminopyridine (DMAP, **1**), dimethyl acetylenedicarboxylate (**2a**), and *N*-benzyl-5-chloro-3-*p*-methylphenacylideneoxindole (**3a**) in dichloromethane was stirred at room temperature. TLC analysis showed that a three-component reaction occurred in 10 h. After workup and analysis, it was surprising to find that a novel dispirooxindole-fused heterocycle **4a** was produced in 70% yield (Scheme 1). The most unusual feature of the structure of **4a** is that two molecular phenacylideneoxindoles took part in the reaction to construct the dispiro compound. This surprising result is of value to us not only because we are interested in the design of new domino reactions but also because we were unable to find published methods for such a convenient synthesis of this kind of product in the literature. Encouraged by the above-mentioned interesting results, the reaction conditions were examined, including the choice of solvent, temperature, molar ratios of the reactants, and the addition sequence of the substrates; the results are summarized in Table 1. The reaction could not proceed in methanol and ethanol at room temperature, and a very low yield of the product was found in DMF and acetone. On the other hand, a good yield of the product was obtained in nonproton polar solvents such as CH_3CN (65%), toluene (70%), and ethyl acetate (62%), without adding any catalyst. The best result was obtained by carrying out the domino reaction in THF at room temperature for ~6 h with a molar ratio of **1**/**2a**/**3a** = 1:1:1.8 (83% yield).

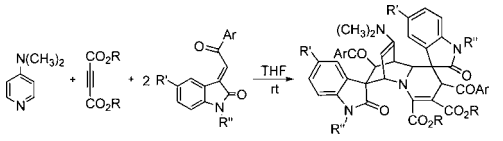
Table 1. Optimizing the Conditions of the Domino Reaction



entry	**1/2a/3a**	solvent	time (h)	yield (%)[a]
1	1:1:2	DMF	10	25
2	1:1:2	DCM	10	73
3	1:1:2	CH_3CN	10	65
4	1:1:2	toluene	10	70
5	1:1:2	acetone	10	trace
6	1:1:2	AcOEt	8	62
7	1:1:2	MeOH	12	–
8	1:1:2	EtOH	12	–
9	1:1:2	THF	6	80
10	1:1:1.8	THF	6	83
11	1:1:1.5	THF	6	78
12	1:1:1	THF	6	70

[a] Isolated yield based on 3-phenacylideneoxindole.

Table 2. Synthesis of Dispirooxindole-Fused Heterocycles[a]



entry	compd	R	R′	R″	Ar	yield[b]
1	**4a**	Me	Cl	$CH_2C_6H_5$	p-$CH_3C_6H_4$	83
2	**4b**	Me	H	$CH_2C_6H_5$	p-ClC_6H_4	80
3	**4c**	Me	Me	$CH_2C_6H_5$	p-ClC_6H_4	85
4	**4d**	Me	F	$CH_2C_6H_5$	p-$CH_3OC_6H_4$	88
5	**4e**	Me	F	$CH_2C_6H_5$	m-$CH_3OC_6H_4$	87
6	**4f**	Me	F	$CH_2C_6H_5$	p-$CH_3C_6H_4$	82
7	**4g**	Me	F	$CH_2C_6H_5$	C_6H_5	79
8	**4h**	Me	Cl	n-C_4H_9	p-$CH_3OC_6H_4$	80
9	**4i**	Me	Cl	n-C_4H_9	p-ClC_6H_4	86
10	**4j**	Me	F	n-C_4H_9	p-$CH_3C_6H_4$	81
11	**4k**	Me	F	n-C_4H_9	p-ClC_6H_4	83
12	**4l**	Et	Cl	$CH_2C_6H_5$	C_6H_5	78
13	**4m**	Et	Cl	$CH_2C_6H_5$	p-ClC_6H_4	89
14	**4n**	Et	F	$CH_2C_6H_5$	p-$CH_3OC_6H_4$	87
15	**4o**	Et	Cl	n-C_4H_9	p-$CH_3C_6H_4$	80

[a] Reaction conditions: DMAP (1.0 mmol), alkyne (1.0 mmol), 3-phenacylideneoxindole (1.8 mmol) in THF (10 mL) at rt for 6 h. [b] Isolated yield.

With the best conditions in hand, we decided to investigate the substrate scope for this domino reaction. Initially, various 3-phenacylideneoxindoles were utilized in the domino reactions under the optimized reaction conditions; the results are shown in Table 2. From these results, we could see that all of the reactions proceeded smoothly to

(12) (a) Esmaeili, A. A.; Vesalipoor, H.; Hosseinabadi, R.; Zavareh, A. F.; Naseri, N. A.; Ghiamati, E. *Tetrahedron Lett*. **2011**, *52*, 4865–4867. (b) Nair, V.; Devipriya, S.; Suresh, E. *Tetrahedron* **2008**, *64*, 3567–3577.

(13) (a) Kiruthika, S. E.; Lakshmi, N. V.; Banu, B. R.; Perumal, P. T. *Tetrahedron Lett*. **2011**, *52*, 6508–6511. (b) Sun, J.; Sun, Y.; Xia, E. Y.; Yan, C. G. *Eur. J. Org. Chem*. **2012**, 1976–1983.

(14) (a) Yang, H. B.; Guan, X. Y.; Wei, Y.; Shi, M. *Eur. J. Org. Chem*. **2012**, 2792–2800. (b) Kiruthika, S. E.; Amritha, R.; Perumal, P. T. *Tetrahedron Lett*. **2012**, *53*, 3268–3273.

(15) (a) Badillo, J. J.; Arevalo, G. E.; Fettinger, J. C.; Franz, A. K. *Org. Lett*. **2011**, *13*, 418–421. (b) Tan, B.; Hernandez-Torres, G. R.; Barbas, C. F., III. *J. Am. Chem. Soc*. **2011**, *133*, 12354–12357.

(16) (a) Deng, H. P.; Wei, Y.; Shi, M. *Org. Lett*. **2011**, *13*, 3348–3351. (b) Zhang, X. C.; Cao, S. H.; Wei, Y.; Shi, M. *Chem. Commun*. **2011**, *47*, 1548–1520.

(17) (a) Basavaiah, D.; Reddy, R. K. *Org. Lett*. **2007**, *9*, 57–60. (b) Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc*. **1998**, *120*, 6477–6487. (c) Sebahar, P. R.; Williams, R. M. *J. Am. Chem. Soc*. **2000**, *122*, 5666–5667.

afford the corresponding dispirooxindole-fused heterocycles **4a**–**4k** in satisfactory yields (entries 1–11, 79–88%). All 3-phenacylideneoxindoles had *N*-benzyl or *N*-*n*-butyl groups. The substituents on both the phenacyl unit and 5-methyl-, 5-chloro-, and 5-fluorooxindole had a marginal efffct on the yields. Diethyl acetylenedicarboxylate also reacted efficiently to yield the desired products **4l**–**4o** (entries 12–15, 78–89%). On the other hand, when 3-phenacylideneoxindole without N-substituents were used in this domino reaction, no dispiro compounds were obtained, and a pyridinium salt of the substituted quinoline-4-carboxylate **5** was isolated, which was formed by the ring isomerization of the oxindole ring (see Supporting Information (SI), Scheme S1).

The structures of the prepared dispirooxindole-fused heterocycles **4a**–**4o** were were fully characterized by ^{1}H and ^{13}C NMR, HRMS, and IR spectra and were further confirmed by single-crystal X-ray diffraction studies performed on compounds **4a** (Figure 1) and **4m**. 2D-NMR (H–H COSY and H–C COSY) spectra of compound **4f** helped to assign the chemical shift of the five CH signals of the 1-aza-bicyclo[2.2.2]octene core in the products (see SI). It should be pointed out that the ^{1}H NMR spectra clearly indicated that only one diastereoisomer exists for each product. The crystal structure of **4a** and **4m** showed that the sequential Diels–Alder reaction exclusively resulted in the *exo*-isomer, in which both the aroxyl (arylcarbonyl) group and the aryl group of the oxindole moiety existed in the *exo*-position of the 1-aza-bicyclo[2.2.2]octene core. It is also clearly seen that these two groups exist in the *trans*-position in the initially formed dihydrospiro-[indoline-3,1′-quinolizin] moiety. Thus, this domino multicomponent reaction also showed very high regio- and diastereoselectivity.

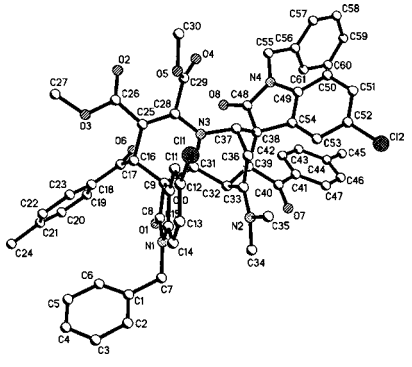
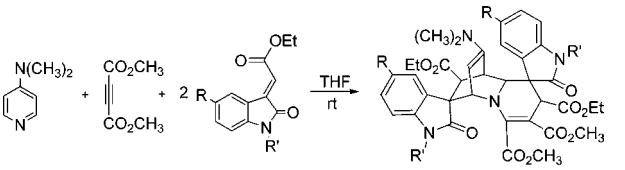


Figure 1. Molecular structure of compound **4a**.

To further illustrate the synthetic value of this protocol, ethyl (3-indolylidene)acetates were employed as one component in the reaction. We are pleased to find that the expected dispirooxindole-fused heterocycles **6a**–**6d** were also obtained in satisfactory yields (Scheme 1).

To extend the utility of this domino reaction, the reactivity of other substituted pyridines was also explored.

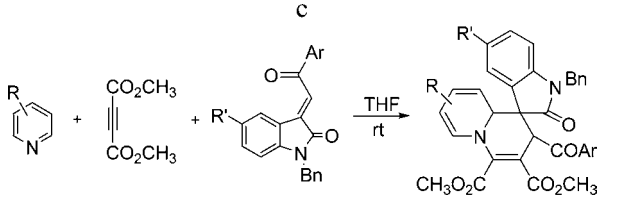
Scheme 1. Synthesis of Dispirooxindoles **6a**–**6d**



6a: R = H, R' = Bn, 78%; **6b**: R = Cl, R' = Bn, 89%
6c: R = F, R' = Bn, 86%; **6d**: R = Cl, R' = Bu, 82%

Under similar reaction conditions, the three-component reactions of dimethyl acetylenedicarboxylate, 3-phenacylideneoxindoles and pyridine, 3-methylpyridine, or 4-methylpyridine gave 2′,9a′-dihydrospiro[indoline-3,1′-quinolizin]-2-one derivatives **7a**–**7d** in good yields (Scheme 2), which were formed by the nomal 1,4-dipolar addition of *in situ* generated Huisgen 1,4-dipoles with 3-phenacylideneoxindoles.[12–14] The further Diels–Alder reaction of spirooxindoles **7a**–**7d** with the second molecule of 3-phenacylideneoxindole did not take place. This may have occurred because the methyl, methoxyl, and acetoamino groups are not sufficiently strong electron-donating groups to activate the cyclic diene unit in spirooxindoles **7a**–**7d** to finish the Diels–Alder reaction. The single crystal structures of **7a** and **7d** (Figure 2) were successfully determined by X-ray diffraction.

Scheme 2. Synthesis of Spirooxindoles **7a**–**7d**



7a: R = H, R' = Cl, Ar = *p*-$CH_3C_6H_4$, 65%
7b: R = 3-CH_3, R'= F, Ar = *p*-$CH_3OC_6H_4$, 74%
7c: R = 3-CH_3, R' = F, Ar = *p*-$CH_3C_6H_4$, 80%
7d: R = 4-CH_3, R' = Cl, Ar = *p*-$CH_3C_6H_4$, 76%

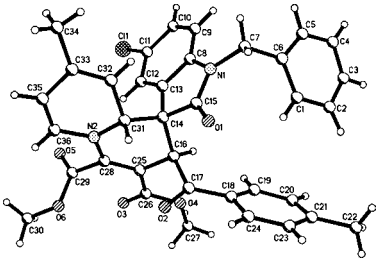
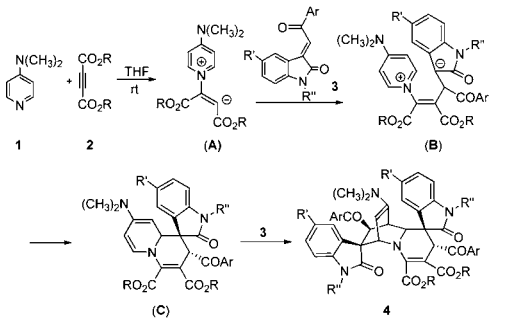


Figure 2. Molecular structure of compound **7d**.

To explain the mechanism of this domino reaction, we have proposed a plausible reaction mechanism (Scheme 3). First, 4-dimethylaminopyridine (**1**) adds to acetylenedicarboxylate (**2**) to give the Huisgen 1,4-dipole intermediate (**A**). Second, the carbanion of intermediate **A** adds to 3-phenacylideneoxindole to form an adduct (**B**).[12−14] Then intramolecular coupling of a carbanium ion with an imine cation gives dihydrospiro[indoline-3,1′-quinolizin]-2-one (**C**). It has been known that the aroxyl group and aryl group of the oxindole moiety exist in the *cis*-position in the starting 3-phenacylideneoxindoles.[17] In the cyclization process the thermodynamically stable *trans*-configuration of the aroxyl group and aryl group of the oxindole moiety was formed by free rotation around the C−C single bond. 3-Phenacylideneoxindoles have been proven to be good dienophiles in some early works.[19] Due to the activation of the strong electron-donating dimethyamino group, the cyclic 1,4-diene unit in adduct **C** readily undergoes the Diels−Alder reaction with the second molecular 3-phenacylideneoxindole to result in the final dispiro compound **4**. In the concerted Diels−Alder reaction the original *cis*-located aroxyl group and aryl group of the oxindole moiety naturally exist in same *exo*-position of the 1-azabicyclo[2.2.2]octene core. In this reaction process, the dimethylamino group plays a very important role by activating the cyclic diene to finish the Diels−Alder reaction. Three similar reactions with pyridine, 3-methylpyridine, and 4-methylpyridine could also finish the 1,4-dipolar addition to give spiro compound **7**, but could not proceed further to the Diels−Alder reaction.

Scheme 3. Formation Mechanism of Dispirooxindole



In summary, we have developed an interesting domino three-component reaction of DMAP, acetylenedicarboxylates, and 3-phenacylideneoxindoles that provides a convenient synthetic procedure for the preparation of complex dispirooxindole-fused heterocycles. Furthermore, the scope and limitation of this reaction were established, which enable further modifications leading to molecular diversity. The short reaction time, readily available substrates, and ease of handling render this domino reaction applicable for the synthesis of structurally diverse heterocyclic compounds. The potential uses of the reaction in synthetic and medicinal chemistry might be quite significant. Further expansion of the reaction scope and synthetic applications of this methodology are in progress in our laboratory

Acknowledgment. This work was financially supported by the National Natural Science Foundation of China (Grant No. 21172189) and the Priority Academic Program Development of Jiangsu Higher Education Institutions.

Supporting Information Available. Experimental procedures and spectral data for all new compounds including crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(18) (a) Autrey, R. L.; Tahk, F. C. *Tetrahedron* **1967**, *23*, 901–917. (b) Kloek, C.; Jin, X.; Choi, K.; Khosla, C.; Madrid, P. B.; Spencer, A.; Raimundo, B. C.; Boardman, P.; Lanza, G.; Griffin, J. H. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2692–2696. (c) Tan, B.; Candeias, N. R.; Barbas, C. F., III. *Nat. Chem.* **2011**, *3*, 473–474.

(19) (a) Long, D. R.; Richards, C. D. *Tetrahedron Lett.* **1975**, 1063–1066. (b) Richards, C. D.; Ross, M. S. F. *Tetrahedron Lett.* **1968**, 14391–4394. Richards, C. D. *Tetrahedron* **1983**, 1817–1821. (d) Okada, K.; Sakuma, H.; Kondo, M.; Snoue, S. *Chem. Lett.* **1975**, 213–216.