ORGANIC
LETTERS

2012
Vol. 14, No. 22
5776–5779

Base-Catalyzed Efficient Tandem [3 + 3] and [3 + 2 + 1] Annulation-Aerobic Oxidative Benzannulations

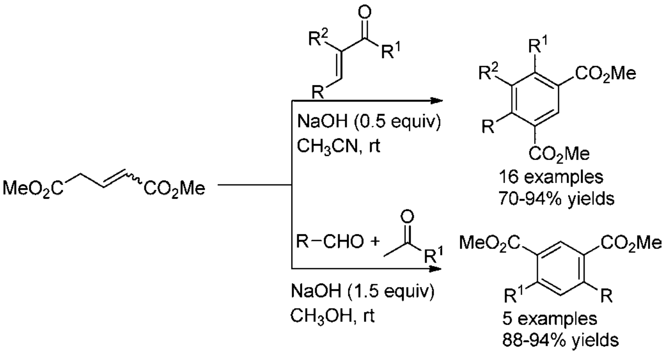
Aboubacar Diallo, Yu-Long Zhao,* He Wang, Sha-Sha Li, Chuan-Qing Ren, and Qun Liu*

Department of Chemistry, Northeast Normal University, Changchun, 130024, P. R. China

zhaoyl351@nenu.edu.cn; liuqun@nenu.edu.cn

Received October 14, 2012

ABSTRACT



An efficient synthesis of substituted benzenes via a base-catalyzed [3 + 3] aerobic oxidative aromatization of α,β-unsaturated carbonyl compounds with dimethyl glutaconate was reported. All the reactions were carried out under mild, metal-free conditions to afford the products in high to excellent yields with molecular oxygen as the sole oxidant and water as the sole byproduct. Furthermore, a more convenient tandem [3 + 2 + 1] aerobic oxidative aromatization reaction was developed through the in situ generation of the α,β-unsaturated carbonyl compounds from aldehydes and ketones.

Substituted arenes are important building blocks in organic synthesis and key constituents of many pharmaceuticals and electronic materials.[1] The utility of these molecules directly reflects the identity and pattern of substituents on the benzene ring,[2] and the regiospecific construction of polysubstituted benzene derivatives with flexible substituent patterns are highly desirable.[1−3] As an efficient alternative to the routes established for the modification of given arenes relying on directed aromatic functionalization (including electrophilic or nucleophilic substitutions, catalyzed coupling, metalation functionalization reactions, etc.),[3] many methods have been developed to construct polysubstituted benzenes from acyclic precursors.[4−11] Although these approaches have each contributed to the development of the synthetic pathway for the synthesis of various substituted benzenes, to our knowledge, there has been no report on the synthesis of polysubstituted benzenes from commercially available starting materials in a single step under mild conditions with the advantage of environmentally benign, atom- and

---

(1) *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: Weinheim, Germany, 2002.

(2) (a) Izawa, Y.; Pun, D.; Stahl, S. S. *Science* **2011**, *333*, 209 (palladium-catalyzed aerobic dehydrogenation of substituted cyclohexanones to phenols). (b) Crone, B.; Kirsch, S. F.; Umland, K.-D. *Angew. Chem., Int. Ed.* **2010**, *49*, 4661 (electrophilic cyclization of 1,5-enynes). (c) Bull, J. A.; Hutchings, M. G.; Quayle, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 1869 (atom-transfer radical cyclization and benzannulation sequences catalyzed by CuCl).

(3) Snieckus, V. *Beilstein J. Org. Chem.* **2011**, *7*, 1215 and references therein.

(4) For recent reviews, see: (a) Serra, S.; Fuganti, C.; Brenna, E. *Chem.—Eur. J.* **2007**, *13*, 6782 (benzannulation of substituted 3,5-hexadienoic acids and 3-alkoxycarbonylhex-3-en-5-ynoic acids). (b) Wessig, P.; Müller, G. *Chem. Rev.* **2008**, *108*, 2051 (the dehydro-Diels−Alder reaction). (c) Dötz, K. H.; Stendel, J., Jr. *Chem. Rev.* **2009**, *109*, 3227 (based on Fischer carbene complexes).

(5) (a) Langer, P. *Synlett* **2009**, 2205 (based on Mukaiyama−Danishefsky−Brassard type reactions). (b) Katritzky, A. R.; Li, J.; Xie, L. *Tetrahedron* **1999**, *55*, 8263 ([3 + 3] benzannulations of benzenoid and heteroaromatic ring systems).

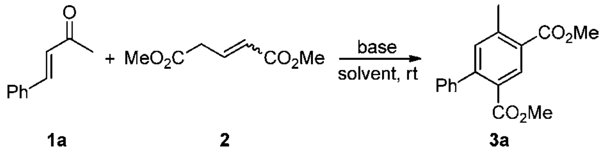
10.1021/ol302829f

energy-efficient processes that do not rely on toxic/precious metals.

During the course of our research, we have investigated the base-mediated [5 + 1] benzannulation[9a] of alkenoyl ketene dithioacetals or analogues with nitro alkanes[9b] or aryl methyl ketones,[9c] [4 + 2] benzannulation of cyclobutenones and active methylene ketones,[10] and [4 + 1 + 1] oxidative benzannulation of acetyl ketene dithioacetals, aromatic aldehydes, and aryl methyl ketones in aerobic conditions.[11] In a recent study, it was found that a series of polysubstituted benzenes can be easily prepared through a base-catalyzed [3 + 3] aerobic oxidative benzannulation of α,β-unsaturated carbonyl compounds with dimethyl glutaconate. The process proceeded under the catalysis of sodium hydroxide at room temperature with the use of aerial oxygen as the oxidant and afforded the products in high to excellent yields. Furthermore, a more convenient tandem [3 + 2 + 1] aerobic oxidative benzannulation reaction was developed through the in situ generation of the α,β-unsaturated carbonyl compounds from aldehydes and ketones. We report here these new results, which allow quick and atom-economical assembly of substituted benzene derivatives from inexpensive and readily available materials and tolerate a broad range of functional groups.

α,β-Unsaturated carbonyl compounds are readily available precursors. However, to the best of our knowledge, the direct formation of multisubstituted benzenes via [3 + 3] benzannulation with α,β-unsaturated carbonyl compounds as 1,3-dielectrophiles has rarely been reported and α,β-unsaturated aldehydes are less effective precursors.[5,6] In addition, an equivalent oxidant (for example $Cu(OAc)_2$) and harsh reaction conditions are generally required.[6b] In the present study, initially, the model reaction of (*E*)-4-phenylbut-3-en-2-one **1a** (1.0 mmol) with dimethyl glutaconate **2** (1.2 mmol) was examined carefully to optimize the reaction conditions (Table 1). Indeed, the [3 + 3] benzannulation reaction of **1a** with **2** could easily proceed to give the polysubstituted benzene **3a** in 93% yield in the presence of NaOH (0.5 equiv) in CH_3CN (5.0 mL) within 15 min in open air (Table 1, entry 2). Interestingly, either decreasing or increasing the amount of NaOH led to lower yields of **3a** (Table 1, entries 1 and 3). In comparison, other bases such as DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) and K_2CO_3 were less (Table 1, entry 4) or not effective (Table 1, entry 5). Among the solvents tested, acetonitrile seemed to be the best choice (Table 1, entry 2). Other solvents, such as THF, DMF, DMSO, and 1,4-dioxane, gave lower product yields (Table 1, entries 6–9). In comparison, no desired product **3a** could be detected when the reaction was carried out in dichloromethane (DCE, Table 1, entry 10).

Table 1. Optimization of Reaction Conditions



entry	base (equiv)	solvent	time (min)	yield[a] (%)
1	NaOH (0.4)	CH_3CN	15	73
2	*NaOH (0.5)*	*CH_3CN*	*15*	*93*
3	NaOH (0.6)	CH_3CN	15	70
4	K_2CO_3 (0.5)	CH_3CN	35	85
5	DBU (0.5)	CH_3CN	180	0
6	NaOH (0.5)	THF	30	70
7	NaOH (0.5)	DMF	60	58
8	NaOH (0.5)	DMSO	60	68
9	NaOH (0.5)	1,4dioxane	60	66
10	NaOH (0.5)	DCE	180	0

[a] Isolated yields.

Next, under the optimal conditions (Table 1, entry 2), the scope of the reaction was investigated by the reaction of dimethyl glutaconate **2** with selected α,β-unsaturated carbonyl compounds **1**, and the results are summarized in Table 2. It is obvious that the tandem reaction showed broad tolerance for various α,β-unsaturated carbonyl substrates **1**. All of selected substrates **1a**–**k**, bearing phenyl (entry 1), electron-deficient (entries 2–5), electron-rich aryl (entries 6–8), heteroaryl (entry 9), phenylvinyl (entry 10), and alkyl (entry 11) R groups at the β-position of the enone moiety, reacted smoothly with dimethyl glutaconate **2** to give the corresponding polysubstituted benzenes **3a**–**k** in high to excellent yields under very mild conditions within 10 to 90 min. Similarly, the desired substituted benzenes **3l** and **3m** were prepared in 80% and 88% yields via the [3 + 3] benzannulation of **1l**

---

(6) For recent reports on [3 + 3] benzannulations, see: (a) Ballini, R.; Palmieri, A.; Barboni, L. *Chem. Commun.* **2008**, 2975 (nitroalkanes as precursors for the synthesis of benzene derivatives). (b) Li, L.; Zhao, M.-N.; Ren, Z.-H.; Li, J.-L.; Guan, Z.-H. *Org. Lett.* **2012**, *14*, 3506 (between enamines and enones). (c) Park, D. Y.; Lee, K. Y.; Kim, J. N. *Tetrahedron Lett.* **2007**, *48*, 1633 (between Baylis–Hillman adducts and 1,3-dinitroalkanes serving as 1,3-dinucleophiles). (d) Langer, P.; Bose, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4033 (between 1,3-bis(silyl enol ether)s and 1,1-diacetylcyclopropane). (e) Song, X.; Zhang, X.; Zhang, S.; Li, H.; Wang, W. *Chem.—Eur. J.* **2012**, *18*, 9770 (synthesis of 3,4-disubstituted benzaldehydes by dimerization of two enals).

(7) For recent reports on [3 + 2 + 1] benzannulations, see: (a) Zhao, W.; Zhang, J. *Org. Lett.* **2011**, *13*, 688 (between diyne-enone and carbon monoxide in the presence of rhodium catalyst). (b) Majumdar, N.; Korthals, K. A.; Wulff, W. D. *J. Am. Chem. Soc.* **2012**, *134*, 1357 (between the α,β-unsaturated Fischer carbene complex of chromium and propargyl ether and carbonoxide). (c) Offner, J. D.; Schnakenburg, G.; Rose-Munch, F.; Rose, E.; Dötz, K. H. *Inorg. Chem.* **2011**, *50*, 8153. (d) Li, C.; Zhang, H.; Feng, J.; Zhang, Y.; Wang, J. *Org. Lett.* **2010**, *12*, 3082 (between tethered ene- and yne-cyclopropenes and carbonoxide in the presence of a rhodium catalyst).

(8) For reports on the multicomponent synthesis of polysubstituted benzenes, see: (a) Xin, X.; Wang, Y.; Xu, W.; Lin, Y.; Duan, H.; Dong, D. *Green Chem.* **2010**, *12*, 893 (between chalcones, malononitrile and/or nitroethane in guanidinium ionic liquids). (b) Yan, C. G.; Song, X. K.; Wang, Q. F.; Sun, J.; Siemeling, U.; Bruhn, C. *Chem. Commun.* **2008**, 1440 (from ethyl α-bromoacetate, aromatic aldehydes, and malononitrile in the presence of pyridine (5 equiv) with 31–46% yields).

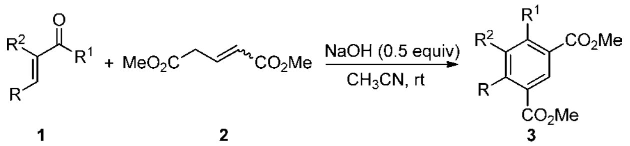
(9) For a recent review on [5 + 1] annulation, see: (a) Pan, L.; Liu, Q. *Synlett* **2011**, 1073. (b) Bi, X.; Dong, D.; Liu, Q.; Pan, W.; Zhao, L.; Li, B. *J. Am. Chem. Soc.* **2005**, *127*, 4578. (c) Fu, Z.; Wang, M.; Dong, Y.; Liu, J.; Liu, Q. *J. Org. Chem.* **2009**, *74*, 6105.

(10) Han, X.-D.; Zhao, Y.-L.; Meng, J.; Ren, C.-Q.; Liu, Q. *J. Org. Chem.* **2012**, *77*, 5173.

(11) Wang, M.; Fu, Z.; Feng, H.; Dong, Y.; Liu, J.; Liu, Q. *Chem. Commun.* **2010**, *46*, 9061.

(R^1 = Et, entry 12) and **1m** (R^1 = Ph, entry 13) with **2**, respectively. Moreover, the reaction of α,β-unsaturated aldehyde **1n** (R^1 = H) could also give the desired product **3n** in 70% yield in the presence of stoichiometric amounts of NaOH at 50 °C in 120 min (entry 14). In addition, in the cases of substrates **1o** and **1p** bearing an acetyl or ethoxycarbonyl group, the reaction could work well, yielding the desired polysubstituted benzenes **3o** and **3p** in 70% and 92% yields, respectively (entries 15 and 16). Clearly, the above-mentioned [3 + 3] benzannulation reaction provides a remarkably simple and efficient access to polysubstituted benzenes, and all the α,β-unsaturated carbonyl compounds **1** including α,β-unsaturated aldehyde (entry 14), chalcones (entry 13), and α,β-unsaturated ketones (entries 1–12, 15, and 16) are effective precursors.

Table 2. NaOH-Catalyzed [3 + 3] Benzannulation Reaction of α,β-Unsaturated Carbonyl Compounds **1** with Dimethyl Glutaconate **2**[a]

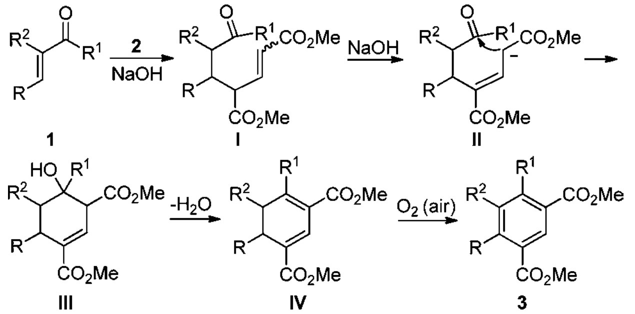


entry	1	R	R^1	R^2	time (min)	product	yield[b] (%)
1	**1a**	C_6H_5	Me	H	15	**3a**	93
2	**1b**	4-ClC_6H_4	Me	H	30	**3b**	93
3	**1c**	4-BrC_6H_4	Me	H	10	**3c**	94
4	**1d**	4-FC_6H_4	Me	H	45	**3d**	93
5	**1e**	4-$NO_2C_6H_4$	Me	H	15	**3e**	88
6	**1f**	4-MeC_6H_4	Me	H	30	**3f**	90
7	**1g**	4-MeOC_6H_4	Me	H	60	**3g**	90
8	**1h**	3,4-$CH_2O_2C_6H_3$	Me	H	60	**3h**	94
9	**1i**	2-furyl	Me	H	60	**3i**	92
10	**1j**	PhCH=CH	Me	H	30	**3j**	92
11[c]	**1k**	C_6H_{11}	Me	H	90	**3k**	80
12	**1l**	C_6H_5	Et	H	90	**3l**	80
13[d]	**1m**	C_6H_5	C_6H_5	H	60	**3m**	88
14[e]	**1n**	C_6H_5	H	H	120	**3n**	70
15[f]	**1o**	C_6H_5	Me	COMe	120	**3o**	70
16[g]	**1p**	C_6H_5	Me	CO_2Et	150	**3p**	92

[a] Reaction conditions: **1** (1.0 mmol), **2** (1.2 mmol), NaOH (0.5 mmol), CH_3CN (5.0 mL), room temperature. [b] Isolated yields. [c] The reaction was performed at 50 °C. [d] The reaction was performed at 30 °C. [e] The reaction was performed in the presence of NaOH (1.0 equiv) at 50 °C. [f] The reaction was performed at 60 °C. [g] The reaction was performed at 70 °C.

On the basis of the above experimental results together with the related reports,[6b,9–13] a possible mechanism for the based-catalyzed [3 + 3] oxidative benzannulation reaction between α,β-unsaturated carbonyl compounds **1** with dimethyl glutaconate **2** is proposed in Scheme 1. In the presence of NaOH, the reaction starts from the intermolecular Michael addition of **2** to **1** to give the intermediate **I**.[9] Subsequently, the intermediate **II**, generated via C=C double bond isomerization of intermediate **I** under basic conditions, undergoes an intramolecular aldol cyclization to afford the six-membered alcohol intermediate **III**.[12] Finally the benzannulation product **3** is formed via a sequential dehydration (**III**→**IV**) and oxidative aromatization with molecular oxygen (from air) process (**IV**→**3**, Scheme 1).[6e,11,13]

Scheme 1. Proposed Mechanism for Formation of Benzenes **3**



Multicomponent reactions (MCRs), the reactions in which several components are combined in sequence, and without isolation of intermediates, are greatly sought because of the inherent molecular diversity, efficiency, and atom economy.[8,11,14,15] In contrast to the rapid development of benzannulation reactions,[1–13] only limited examples of [3 + 2 + 1] benzannulation have been reported[7] and, to date, [3 + 2 + 1] benzannulations using three different precursors have rarely been reported except for the case limited to the combination of chalcone, malononitrile, and nitroethane.[8a] Prompted by the success of the remarkably simple and efficient [3 + 3] benzannulation reaction (Table 1 and Scheme 1) and combined with the consideration of the significant advantages of multicomponent reactions (MCRs),[14] a three-component reaction ([3 + 2 + 1] benzannulation) combined with the in situ generation of a Michael acceptor under basic conditions was examined. To our delight, after optimization of the reaction conditions, it was found that the three-component reaction of aldehydes **4**, ketones **5**, and dimethyl glutaconate **2** can proceed smoothly in the presence of 1.5 equiv of NaOH in CH_3OH within 65–180 min to give the corresponding polysubstituted benzenes **3b**, **3m**, and **3q**–**s** in high to excellent yields (Table 3, entries 1–5).

---

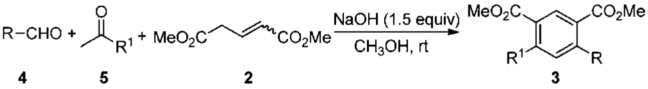
(12) Kiren, S.; Padwa, A. *J. Org. Chem.* **2009**, *74*, 7781.

(13) (a) Xie, P.; Huang, Y.; Chen, R. *Chem.—Eur. J.* **2012**, *18*, 7362. (b) Nandaluru, P. R.; Bodwell, G. J. *Org. Lett.* **2012**, *14*, 310. (c) Gioia, C.; Fini, F.; Mazzanti, A.; Bernardi, L.; Ricci, A. *J. Am. Chem. Soc.* **2009**, *131*, 9614.

(14) For recent reviews, see: (a) Groenendaal, B.; Ruijter, E.; Orru, R. V. A. *Chem. Commun.* **2008**, 5474. (b) Tejedor, D.; García-Tellado, F. *Chem. Soc. Rev.* **2007**, *36*, 484. (c) Touré, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439. (d) Ganem, B. *Acc. Chem. Res.* **2009**, *42*, 463.

(15) Li, Y.; Xu, X.; Tan, J.; Xia, C.; Zhang, D.; Liu, Q. *J. Am. Chem. Soc.* **2011**, *133*, 1775.

Table 3. Three-Component [3 + 2 + 1] Benzannulation Reaction of Aldehydes **4**, Ketones **5**, and Dimethyl Glutaconate **2**[a]



entry	R	R^1	time (min)	product	yield[b] (%)
1[c]	C_6H_5	C_6H_5	65	**3m**	88
2	4-ClC_6H_4	C_6H_5	120	**3q**	94
3	4-MeC_6H_4	C_6H_5	120	**3r**	90
4	2-furyl	C_6H_5	180	**3s**	93
5[d]	4-ClC_6H_4	CH_3	80	**3b**	92

[a] Reaction conditions: **2** (1.2 mmol), **4** (1.0 mmol), **5** (1.0 mmol), NaOH (1.5 mmol), CH_3OH (5.0 mL), 65–180 min, room temperature. [b] Isolated yields. [c] The reaction was performed at 30 °C. [d] The reaction was performed at 50 °C.

In summary, we have developed a novel base-catalyzed [3 + 3] aerobic oxidative aromatization of α,β-unsaturated carbonyl compounds with dimethyl glutaconate, which provides a highly facile and efficient method for the rapid construction of polysubstituted benzenes from easily available starting materials in high to excellent yields under mild and metal-free conditions. Most attractively, a more convenient tandem [3 + 2 + 1] aerobic oxidative aromatization reaction was also carried out through the in situ generation of the α,β-unsaturated carbonyl compounds from aldehydes and ketones, thereby greatly improving the reaction efficiency. Further studies are in progress.

Acknowledgment. Financial support from the National Natural Sciences Foundation of China (21172032 and 20972026) is gratefully acknowledged.

Supporting Information Available. Experimental procedures, NMR spectra, and characterization data for new compounds **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.