ORGANIC LETTERS

2006
Vol. 8, No. 22
5061−5064

Intermolecular Tandem Addition–Cyclization of Bromoallenes: A Facile Synthesis of Methylenecyclopropyl Carboxylates and Polysubstituted Furans

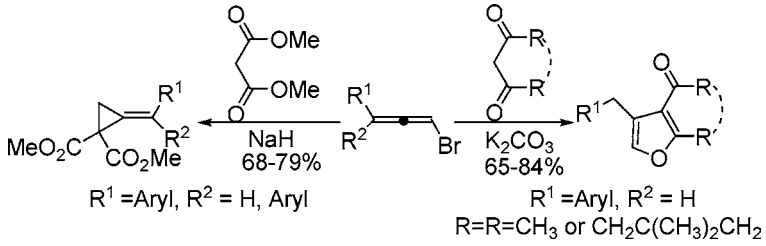
Lubin Xu,[†] Xian Huang,*[,†,‡] and Fangrui Zhong[†]

Department of Chemistry, Zhejiang University (Xixi Campus), Hangzhou 310028, PRC, and State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, PRC

huangx@mail.hz.zj.cn

Received August 10, 2006

ABSTRACT



The base-mediated reactions of 1,3-dicarbonyl compounds with bromoallenes used as an allyl dication equivalent were explored. The corresponding dimethyl methylenecyclopropane-1,1-dicarboxylates and 2,3,4-trisubstituted furans were efficiently synthesized.

Reactions of bromoallenes have attracted much interest in recent years because of the interesting chemical properties associated with their cumulated double bonds and bromine atom.[1−5] More recently, Tanaka reported[6] the tandem intramolecular cyclization of nitrogen binucleophilic reagents with bromoallenes which act as allyl dication equivalents, affording a very useful process for the synthesis of medium-sized heterocycles. However, the intermolecular tandem cyclizations of bromoallenes as allyl dication equivalents to form carbocycles or heterocycles have not been reported yet. This promoted us to investigate the intermolecular cyclization of bromoallenes with nucleophilic reagents.

Dimethyl malonate was chosen as a nucleophilic reagent for our initial study on the intermolecular cyclization of bromoallenes. We postulated a possible pathway of the

[†] Zhejiang University (Xixi Campus).
[‡] Chinese Academy of Sciences.

(1) *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds; Wiley-Vch: Weinheim, 2004; Vol. 2.

(2) For organocopper-mediated substitutions, see examples: (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1984**, *25*, 3059. (b) Caporusso, A. M.; Polizzi, C.; Lardicci, L. *Tetrahedron Lett.* **1987**, *28*, 6073. (c) D'Aniello, F.; Mann, A.; Taddei, M. *J. Org. Chem.* **1996**, *61*, 4870. (d) Chemla, F.; Bernard, N.; Normant, J. *Eur. J. Org. Chem* **1999**, 2067. (e) Conde, J. J.; Mendelson, W. *Tetrahedron Lett.* **2000**, *41*, 811. (f) Caporusso, A. M.; Zampieri, A.; Aronica, L. A.; Banti, D. *J. Org. Chem.* **2006**, *71*, 1902.

(3) For palladium-catalyzed cross-coupling reactions, see: (a) MLrkl, G.; Attenberger, P.; Kellner, J. *Tetrahedron Lett.* **1988**, *29*, 3651. (b) Gillmann, T.; Hülsen, T.; Massa, W.; Wocadlo, S. *Synlett* **1995**, 1257. (c) Saalfrank, R. W.; Haubner, M.; Deutscher, C.; Bauer, W.; Clark, T. *J. Org. Chem.* **1999**, *64*, 6166.

(4) For the formation of nucleophilic allenyl metal reagents, see: (a) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1997**, *62*, 8976. (b) Ma, S.; Yu, S.; Yin, S. *J. Org. Chem.* **2003**, *68*, 8996.

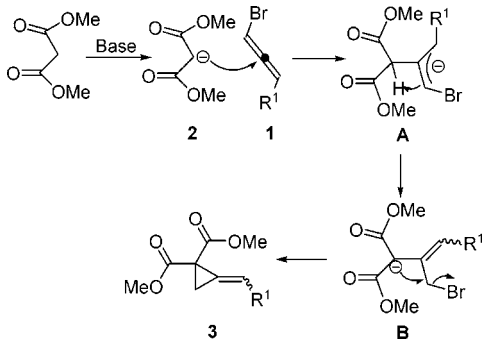
(5) For ring-forming reactions, see: (a) Ohno, H.; Hamaguchi, H.; Tanada, T. *Org. Lett.* **2001**, *3*, 2269. (b) Ohno, H.; Ando, K.; Hamaguchi, H.; Takeoka, Y.; Tanaka, T. *J. Am. Chem. Soc.* **2002**, *124*, 15255.

(6) (a) Ohno, H.; Hamaguchi, H.; Ohata, M.; Tanaka, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 1749. (b) Ohno, H.; Hamaguchi, H.; Ohata, M.; Kosaka, S.; Tanaka, T. *Heterocycles* **2003**, *61*, 65. (c) Ohno, H.; Hamaguchi, H.; Ohata, M.; Kosaka, S.; Tanaka, T. *J. Am. Chem. Soc.* **2004**, *126*, 8744. (d) Hamaguchi, H.; Kosaka, S.; Ohno, H.; Tanaka, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 1513.

10.1021/ol061993u CCC: $33.50 © 2006 American Chemical Society
Published on Web 09/29/2006

tandem reaction (Scheme 1). The carbanion **2** might attack

Scheme 1. Proposed Reaction Process of Dimethyl Malonate with Bromoallene in the Presence of a Base

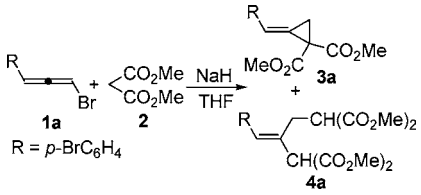


the central carbon atom of bromoallene **1** to form the allyl carbanion intermediate, and then intramolecular hydrogen transfer would give a new carbanion **B** containing an allylic bromide moiety, which may undergo an intramolecular nucleophilic substitution to produce the methylenecyclopropane-1,1-dicarboxylate **3**. If it could be realized smoothly, the tandem reaction would afford a novel and efficient method for the synthesis of methylenecyclopropanes (MCPs) with two carbonyl groups on the three-membered carbocycle. These MCPs are very useful building blocks in organic synthesis,[7] and some of their nucleoside derivatives show important antiviral and anti-HIV-1 activities.[8,9] Compared with the methods for synthesis of these MCPs in the literature,[7,8] our method presented here would require neither the expensive transition-metal catalysts nor long reaction steps.

Initial efforts focused on the treatment of dimethyl malonate (1.0 mmol) with 3-(*p*-bromophenyl)bromoallene **1a**[10] (1.0 mmol) in the presence of NaH (50%, 1.0 mmol). Luckily, the desired dimethyl 2-(4-bromobenzylidene)cyclopropane-1,1-dicarboxylate **3a** was isolated in 65% yield together with the product **4a** in 19% yield (entry 1, Table 1). The formation of **4a** most likely occurs by the intermediate **A** (Scheme 1) undergoing subsequent intermolecular hydrogen transfer with dimethyl malonate and intermolecular nucleophilic substitution to give **4a**.

Considering the forming process of **4a**, we reckon that increasing the amount of bromoallene may avoid the formation of **4a**. So, we changed the amount of bromoallene and studied the temperature effect. From the results in Table 1,

Table 1. Addition−Cyclization of Dimethyl Malonate **2** with **1a** Under Different Conditions[a]



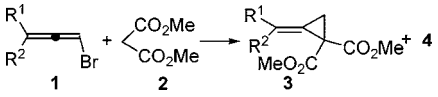
entry	bromoallene (equiv)	temp (°C)	time (h)	yield[b] (%) of **3a/4a**
1	1.0	rt	56	65/19
2	1.2	rt	53	69/14
3	1.2	40	38	71/13
4	1.2	55	26	73/11
5	1.5	55	24	76/7
6	1.8	55	24	76/6
7[c]	1.5	reflux	20	73/5

[a] Reagents and conditions: 1mmol of **2** and 1 mmol of NaH (50%) in 6 mL of THF, N_2. [b] Isolated yield. [c] Unidentified compound was observed.

it should be noted that the yield of **3a** and the selectivity of the reaction were both improved when the reaction was conducted using 1.5 equiv of bromoallene **1a** at 55 °C (entry 5, Table 1). However, adding up to 1.8 equiv of **1a** failed to increase the yield of **3a** remarkably (entry 6, Table 1). It also should be pointed out that the reaction at a temperature higher than 55 °C produced an unidentified compound (entry 7, Table 1). Thus, we chose 1.5 equiv of bromoallene and a temperature of 55 °C as suitable reaction conditions.

With the optimized reaction conditions in hand, the scope and the limitation of this reaction were examined. Some typical results are summarized in Table 2. We were pleased

Table 2. Intermolecular Tandem Addition−Cyclization of **2** with Arylbromoallenes **1** Affording **3**[a]



	1		time	yield of
entry	R^1	R^2	(h)	**3/4** (%)
1	**1a**, *p*-BrC_6H_4	H	24	**3a/4a** (76/7)
2	**1b**, *p*-ClC_6H_4	H	22	**3b**/**4b** (73/8)
3	**1c**, C_6H_5	H	28	**3c/4c** (70/8)
4	**1d**, *p*-FC_6H_4	H	20	**3d/4d** (76/6)
5	**1e**, *o*,*o*-$Cl_2C_6H_3$	H	24	**3e/4e** (68[b]/6)
6	**1f**, *p*-$F_3CC_6H_4$	H	20	**3f/4f** (79/5)
7	**1g**, *p*-$CH_3C_6H_4$	H	38	**3g/4g** (−[c]/6)
8[d]	**1h**, C_6H_5	C_6H_5	36	**3h/4h** (74/8)
9[d]	**1i**, *p*-ClC_6H_4	*p*-ClC_6H_4	36	**3i/4i** (76/7)
10[d]	**1j**, *p*-FC_6H_4	*p*-FC_6H_4	32	**3j/4j** (78/5)

[a] Reagents and Conditions: 1.5 mmol of **1**, 1.0 mmol of **2**, and 1.0 mmol of NaH (50%) in 6 mL of THF at 55 °C, N_2. [b] Accompanied with 14% uncertain byproduct. [c] Unidentified mixture. [d] Reaction temp at 60 °C.

to find that both monosubstituted and disubstituted arylbro-

(7) (a) Singleton, D. A.; Huval, C. C. *J. Org. Chem.* **1994**, *59*, 2020. (b) Ma, S.; Zhang, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 183. (c) Ma, S.; Lu, L.; Zhang, J. *J. Am. Chem. Soc.* **2004**, *126*, 9645. (d) Ma, S.; Lu, L. *J. Org. Chem.* **2005**, *70*, 7629. (e) Ma, S.; Lu, L.; Chen, G. *Org. Lett.* **2006**, *8*, 835.

(8) Yan, Z. H.; Kern, E. R.; Gullen, E.; Cheng, Y. C.; Drach, J. C.; Zemlicka, J. *J. Med. Chem.* **2005**, *48*, 91 and references cited therein.

(9) Cheng, C. M.; Shimo, T.; Somekawa, K.; Baba, M. *Tetrahedron* **1998**, *54*, 2031.

(10) For the preparation of bromoallenes, see: (a) Landor, S. R.; Patel, A. N.; Whiter, P. F.; Greaves, P. M. *J. Chem. Soc. (C)* **1966**, 1223. (b) Elsevier, C. J.; Vermeer, P.; Gedanken, A.; Runge, W. *J. Org. Chem.* **1985**, *50*, 364.

moallenes could lead to the corresponding bis(methoxycarbonyl)-2-arylmethylidenecyclopropanes **3**. For the mono- or diaryl substituted bromoallenes, introducing an electron-withdrawing group (or atom) to the aryl ring may favor the reaction because of the fact that electropositivity of the central carbon on bromoallenes may be increased (**3a**,**b**, entries 1 and 2; **3d**−**f**, entries 4−6 and 8−10, Table 2). For the diaryl substituted bromoallenes, a longer reaction time was needed (entries 8−10, Table 2).

The configuration of the C═C bond in the products **3a**−**f** was assigned on the basis of NOESY and X-ray diffraction studies of **3a** (Figure 1).[11] The NOESY spectra of **3a** show

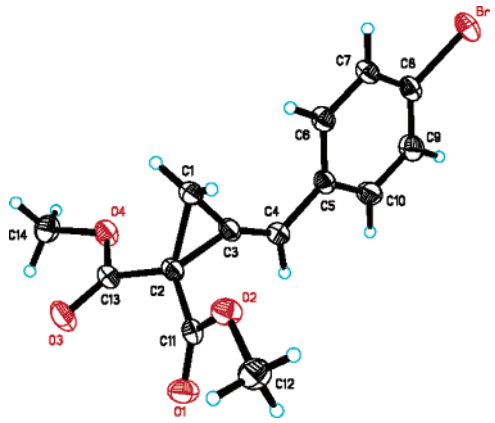


Figure 1. X-ray crystal structure of **3a**.

that there is a correlation between the methylene protons of the three-membered ring and the protons on the phenyl group. From Figure 1, we can see that the bromophenyl group is cis oriented with the methylene of the three-membered ring. These results demonstrate that the configuration of the C═C bond in **3a** is *E*-form.

The reaction of an alkylbromoallene, such as 3-hexylbromoallene, with dimethyl malonate was run at the same conditions; however, we did not obtain the corresponding addition−cyclization product but instead obtained dimethyl 2-(non-1-yn-3-yl)malonate in 53% yield via a S_N2' reaction process.[12]

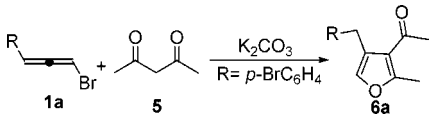
Under similar conditions, the reaction of bromoallene **1a** with 2,4-pentadione **5** as a nucleophile was performed. However, we did not isolate the desired methylenecyclopropyl ketone but obtained an unexpected 2,3,4-trisubstituted furan **6a** in 23% yield (entry 1, Table 3).

As shown in Scheme 2, the diketone carbanion **D** existing in its enol form undergoes intramolecular nucleophilic

(11) X-ray data for compound **3a**: $C_{14}H_{13}BrO_4$, MW = 372.14, triclinic, space group *P*1, final *R* indices [$I > 2\sigma(I)$], R1 = 0.0569, wR2 = 0.1335, a = 7.9280 (13) Å, b = 7.9969 (13) Å, c = 1.261 (2) Å, α = 83.526 (3)°, β = 78.836 (3)°, γ = 62.414 (3)°, V = 675.72 (19) Å^3, T = 293(2) K, Z = 2, D_c = 1.598 g/cm^{-1}, μ = 3.048 mm^{-1}, λ = 0.71073Å, reflections collected/unique, 3979/2867 (R_{int} = 0.1195), parameters 187. GOF on F^2 = 0.951.

(12) Intra- or intermolecular S_N2' reaction about bromoallenes. See examples in refs 2 and 5.

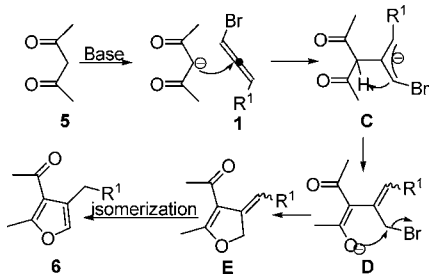
Table 3. Optimization of Reaction of **1a** with 2,4-Pentadione **5** Used as a Binucleophilic Reagent[a]



entry	**1a** (equiv)	Bu_4NBr (equiv)	solvent	time (h)	yield (%)[b]
1[c]	1.5	0	THF	54	23
2	1.2	0	THF	60	14
3	1.2	0.1	THF	60	18
4	1.2	0	DMF	60	22
5	1.2	0.1	DMF	60	28
6	1.2	0	acetone	56	48
7	1.2	0.1	acetone	46	64
8	1.5	0.1	acetone	46	64
9	1.2	0.2	acetone	42	73
10	1.5	0.2	acetone	42	73
11	1.2	0.3	acetone	42	73

[a] Reagents and conditions: 1.0 mmol of **5** and 1.0 mmol of base in 8 mL of solvent at 55 °C. [b] Isolated yield based on **5**. [c] Using NaH as base.

Scheme 2. Possible Reaction Process of 1,3-Diketone with Bromoallene under the Basic Conditions



substitution via the attack of the oxygen to offer the five-membered intermediate **E**, which finally isomerizes to the more stable polysubstituted furan **6**.

Because 1,3-diketones are more acidic than malonate esters, a base weaker than NaH might also be suitable for the reaction and K_2CO_3 was used instead. Considering the reaction proceeded between liquid and solid phases, it might be improved by adding a suitable amount of phase-transfer catalyst, thus tetrabutylammonium bromide was used. So, various reaction conditions including the solvent and the amount of bromoallene and tetrabutylammonium bromide were tested. Some typical results are summarized in Table 3. According to Table 3, the optimized conditions are as follows: 1.0 equiv of K_2CO_3, 1.2 equiv of **1a**, and 0.2 equiv of tetrabutylammonium bromide in acetone.

Then, the reaction of monoarylbromoallenes **1a**−**f** with 2,4-pentadione **5** and 5,5-dimethylcyclohexane-1,3-dione **7** was tested and summarized in Table 4. In Table 4, all the reactions proceeded smoothly to give desired furans in good yields. A similar effect of the substituted groups on the aryl ring was also observed. Both the rate and yield were slightly

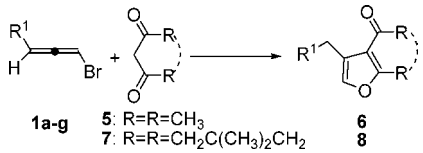
improved when there was an electron-withdrawing group (or atom) on the aryl ring (compare entries 1−4 and 7−12 with entries 5 and 6, Table 4). However, this reaction did not occur when an electron-donating group was introduced to the aryl ring (entry 13, Table 4). The reactions of diarylbromoallene **1h**−**j** with 2,4-pentadione **5** under similar conditions also failed to give the desired furans. When we tried to extend this protocol to alkylbromoallenes, unluckily, no reaction occurred.

Polysubstituted furans play an important role in organic chemistry not only due to their presence as key structural units in many natural products and important pharmaceuticals but also because they can be employed in synthetic chemistry as versatile building blocks.[13,14] Thus, our method afforded a simple and efficient method for the synthesis of 2,3,4-trisubstituted furans.[15]

In conclusion, we present the first intermolecular tandem addition−cyclization of arylbromoallenes as allyl dication equivalents. The described method provides a simple and efficient method for the synthesis of (*E*)-dimethyl 2-arylmethylidenecyclopropane-1,1-dicarboxylates and 2,3,4-trisubstituted furans by using dimethyl malonate and 1,3-diketones as binucleophilic reagents, respectively.

(13) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795.
(14) *Natural Products Chemistry*; Nkanishi, K., Ed.; Kondasha: Tokyo, 1974.
(15) Some new methods have been reported for the synthesis of densely polysubstituted furans recently. See examples: (a) Ma, S.; Li, L. *Org. Lett.* **2000**, *2*, 941. (b) Stauffer, F.; Neier, R. *Org. Lett.* **2000**, *2*, 3535. (c) Ma, S.; Zhang, J. *Chem. Commun.* **2000**, 117. (d) Nair, N.; Menon, R. S.; Vinod, A. U.; Viji, S. *Tetrahedron Lett.* **2002**, *43*, 2293. (e) Nair, N.; Vinod, A. U.; Abhilash, N.; Menon, R. S.; Santhi, V.; Varma, R. L.; Viji, S.; Mathew, S.; Srinivas, R. *Tetrahedron* **2003**, *59*, 10279. (f) Yavari, I.; Alizadeh, A.; Anary-Abbasinejad, M.; Bijanzadeh, H. R. *Tetrahedron* **2003**, *59*, 6083. (g) Aurrecoechea, J. M.; Perez, E. *Tetrahedron Lett.* **2003**, *44*, 3263. (h) Azizian, J.; Mohammadi, A. A.; Karimi, A. R. *Heteroatom Chem.* **2005**, *16*, 259. (i) Ma, S.; Zhang, J. *J. Am. Chem. Soc.* **2003**, *125*, 12386. (j) Zhou, C. Y.; Chan, P. W. H.; Che, C. M. *Org. Lett.* **2006**, *8*, 325.

Table 4. Intermolecular Tandem Addition−Cyclization of 1,3-Diketone with Arylbromoallenes **1a**−**f** Affording Polysubstituted Furans[a]



entry	arylbromoallene	1,3-diketone	time (h)	yield (%)[b]
1	**1a**	**5**	42	**6a** (73)
2		**7**	54	**8a** (68)
3	**1b**	**5**	46	**6b** (71)
4		**7**	54	**8b** (66)
5	**1c**	**5**	46	**6c** (71)
6		**7**	56	**8c** (65)
7	**1d**	**5**	40	**6d** (76)
8		**7**	50	**8d** (69)
9	**1e**	**5**	28	**6e** (80)
10		**7**	46	**8e** (73)
11	**1f**	**5**	26	**6f** (84)
12		**7**	45	**8f** (75)
13	**1g**	**5**	60	NR

[a] Reagents and conditions: 1.2 mmol of bromoallene, 1.0 mmol of **5** (or **7**), 1.0 mmol of K_2CO_3, 0.2 equiv of PTC in 8 mL of acetone. [b] Isolated yield based on **5** (or **7**).

Acknowledgment. We are grateful to the National Natural Science Foundation of China (Project No. 20472072, 20332060) for financial support.

Supporting Information Available: Crystallographic information files (CIF) for **3a** and experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL061993U