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# Formal [4 + 1]- and [5 + 1]-Annulation by an $S_N2$–Conjugate Addition Sequence: Stereoselective Synthesis of Highly Substituted Carbocycles

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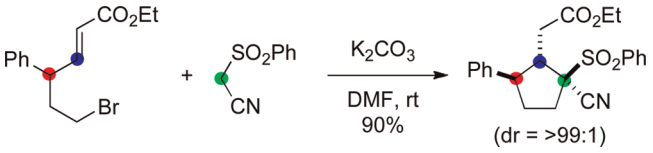
## ABSTRACT




**$K_2CO_3$-mediated reactions of 6-bromo-2-hexenoates and 7-bromo-2-heptenoate with active methylene compounds deliver highly substituted cyclopentane and cyclohexane derivatives, respectively via a sequence of $S_N2$–conjugate addition reactions (formal [4 + 1]- and [5 + 1]-annulation) in a diastereoselective manner.**

Stereo- and regioselective construction of five- and six-membered carbocycles (cyclopentane and cyclohexane derivatives) is one of the most fundamental and important issues in synthetic organic chemistry because of the importance and prevalence of these motifs in many biologically active natural products and drug molecules.[1] Intermolecular annulation reactions allow for the rapid and selective construction of complex cyclic structures in a one-pot manner from relatively simple building blocks, which is one of the most ideal processes in organic synthesis from atom-[2] and step-economical[3] points of view. While the annulation approaches to construct cyclopentane and cyclohexane derivatives have typically relied on the [3 + 2]-[4] and [4 + 2]-modes[5] (cycloaddition),[6] respectively, the corresponding [4 + 1]-[7] and [5 + 1]-processes[8] are scarce. Guided by these views as well as our current interest in conjugate addition reactions[9] of carbon nucleophiles

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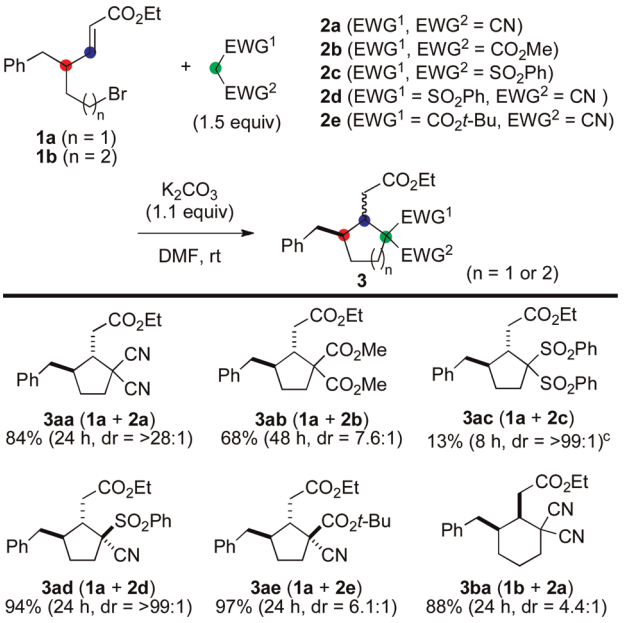
toward acrylate derivatives,[10] we became interested in the base-mediated reaction of 6-halo-2-hexenoates and 7-halo-2-heptenoates with active methylene compounds that would provide cyclopentane and cyclohexane derivatives, respectively, via a sequence of $S_N2$−conjugate addition (a formal [4 + 1]- and [5 + 1]-annulation).[11−13] Herein, we report a study of this strategy on the carbocycle synthesis in terms of the reaction efficiency as well as the diastereoselectivity with various substituents.

We began our investigation by studying the $K_2CO_3$-mediated reactions of (*E*)-ethyl 4-benzyl-6-bromo-2-hexenoate (**1a**)[14] with a series of active methylene compounds **2** (Chart 1).[15] Malononitrile (**2a**), dimethylmalonate (**2b**) underwent smooth reactions in DMF at room temperature to afford trisubsituted-cyclopentanes **3aa** and **3ab** in good yields with high 2,3-*trans*-diastereoselectivity. The reaction of bis(phenylsulfonyl)methane (**2c**) was sluggish, giving cyclopentane **3ac** only in 13% yield (in spite of excellent diastereoselectivity) even at a higher temperature of 60 °C. Three successive stereogenic centers were constructed on cyclopentane frameworks **3** using (phenylsulfonyl)acetonitrile (**2d**) and *tert*-butyl cyanoacetate (**2e**). The reaction with **2d** provided a nearly single isomer of **3ad**, while that of **2e** dropped the diastereoselectivity of **3ae**, where the stereochemistry of the major compound was 1,2-*trans*-2,3-*trans*. Interestingly, construction of a cyclohexane ring from (*E*)-ethyl 4-benzyl-7-bromo-2-heptenoate (**1b**) with malononitrile (**2a**) resulted in a reversal of diastereoselectivity that gave 2,3-*cis*-cyclohexane **3ba** as a major product in good yield. However, the reaction of **1b** with dimethyl malonate (**2b**) was very sluggish (70% yield, dr = 2.3:1 for 5 days), and that with (phenylsulfonyl)-acetonitrile (**2d**) gave three inseparable diastereomers with low selectivity while the cyclization proceeded smoothly (93% yield for 24 h, dr = 39:36:25; see Supporting Information).

**Chart 1.** Synthesis of carbocycles by $K_2CO_3$-mediated reactions of **1** with active methylene compounds **2**[a,b]




[a] Unless otherwise noted, the reactions were carried out on the scale of 0.3 mmol of **1** and **2** (1.5 equiv) with $K_2CO_3$ (1.1 equiv) in DMF (3 mL) at rt under a $N_2$ atmosphere. [b] Isolated yields were recorded above. Diastereomer ratio determined by $^1H$ NMR, and the structure of the major isomer shown. [c] The reaction was carried out at 60 °C. The acyclic product obtained only via the $S_N2$ reaction was isolated in 60% yield (see Supporting Information).

Encouraged by the diastereoselective [4 + 1]-annulation to construct cyclopentane, we next set out to investigate the reaction of malononitrile (**2a**) with various 4-substituted 6-bromo-2-hexenoates (Table 1). Methyl (**1c**), methoxymethyl (**1d**), allylic (**1e**), propargylic (**1f**), isopropyl (**1g**), and phenyl (**1h**) moieties could be installed to afford the corresponding cyclopentanes in good to excellent chemical yields with high *trans*-diastereoselectivity.

The construction of cyclopentanes bearing three successive stereogenic centers was also examined using (phenylsulfonyl)acetonitrile (**2d**) with various (*E*)-ethyl 4-benzyl-6-bromo-2-hexenoates **1** (Table 2). The cyclopentanes **3** were obtained in good yields as a nearly single isomer except for the reactions of **1c** and **1d** (entries 1 and 2).

We next examined the effect of the substituents on the other positions of 6-bromo-2-hexenoates **1** for the diastereoselectivity (Schemes 1 and 2). Installation of a phenyl group on the C(5) position of **1i** rendered the diastereoselectivity to be lower, giving trisubsituted cyclopentanes **3ia** and **3ia′** in a 1.7:1 ratio (Scheme 1a). It was found that the reactions of *trans*-4,5-disubstituted 6-bromo-2-hexenoate **1j** with **2a** and **2d** provided tetrasubstituted cyclopentanes **3ja** and **3jd**, respectively, in high diastereoselectivity

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(11) For prior reports on an $S_N2$−conjugate addition sequence, see: (a) Gharpure, S. J.; Reddy, S. R. B. *Tetrahedron Lett.* **2010**, *51*, 6093. (b) Gharpure, S. J.; Reddy, S. R. B. *Org. Lett.* **2009**, *11*, 2519. (c) Gharpure, S. J.; Reddy, S. R. B.; Sanyal, U. *Synlett* **2007**, 1889. (d) Desmaël, D.; Louvet, J.-M. *Tetrahedron Lett.* **1994**, *35*, 2549. (e) Bunce, R. A.; Peeples, C. J.; Jones, P. B. *J. Org. Chem.* **1992**, *57*, 1727.

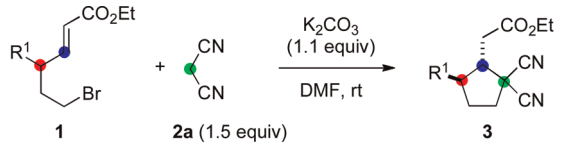
(12) For reports on synthesis of carbocycles by double conjugate addition, see: Kamenecka, T. M.; Overman, L. E.; Ly Sakata, S. K. *Org. Lett.* **2002**, *4*, 79 and references therein.

(13) For reports on the synthesis of carbocycles by a conjugate addition−$S_N2$ sequence, see: Atta, A. K.; Pathak, T. *Eur. J. Org. Chem.* **2010**, 6810 and references therein.

(14) All the starting materials **1** used in this manuscript were prepared from the corresponding lactones as a racemic form; see Supporting Information for more details.

(15) Optimization of the reaction conditions for the present annulation was examined using (*E*)-ethyl 6-bromohex-2-enoate and (phenylsulfonyl)acetonitrile (**2d**), see Supporting Information.

**Table 1.** Reactions with Malononitrile (**2a**)[a]

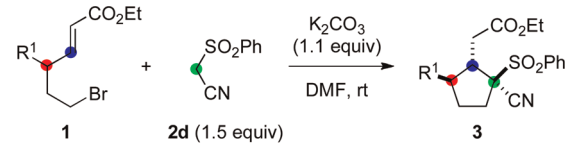



**1** **2a** (1.5 equiv) **3**

| entry | | $R^1$ | time/h | yield[b] | dr[c] |
|---|---|---|---|---|---|
| 1 | **1c** | Me | 9 | **3ca** (84%) | 10:1 |
| 2 | **1d** | MeO | 18 | **3da** (94%) | 12.1:1 |
| 3 | **1e** | | 8 | **3ea** (86%) | 32:1 |
| 4 | **1f** | | 21 | **3fa** (86%) | 35:1 |
| 5 | **1g** | Me, Me | 14 | **3ga** (75%) | 35:1 |
| 6 | **1h** | Ph | 10 | **3ha** (83%) | >99:1 |

[a] Unless otherwise noted, the reactions were carried out on the scale of 0.3 mmol of **1** and 1.5 equiv of **2** in DMF (3 mL) at rt under a $N_2$ atmosphere. [b] Isolated yields were recorded above. [c] The diastereomer ratio was determined by $^1$H NMR.

**Table 2.** Reactions with (Phenylsulfonyl)acetonitrile (**2d**)[a]




**1** **2d** (1.5 equiv) **3**

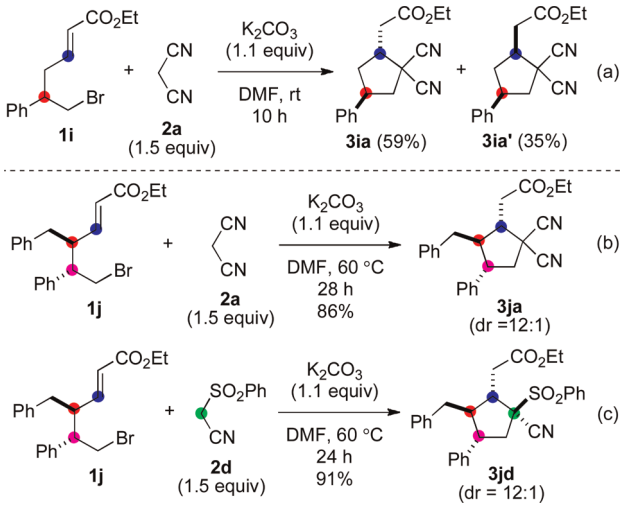
| entry | | $R^1$ | time/h | yield[b] | dr[c] |
|---|---|---|---|---|---|
| 1 | **1c** | Me | 23 | **3cd** (73%) | 8.8:1 |
| 2 | **1d** | MeO | 18 | **3dd** (89%) | 15.7:1 |
| 3 | **1e** | | 19 | **3ed** (87%) | >99:1 |
| 4 | **1f** | | 23 | **3fd** (81%) | >99:1 |
| 5 | **1g** | Me, Me | 14 | **3gd** (78%) | >99:1 |
| 6 | **1h** | Ph | 24 | **3hd** (92%) | >99:1 |

[a] Unless otherwise noted, the reactions were carried out on the scale of 0.3 mmol of **1** and 1.5 equiv of **2** in DMF (3 mL) at rt under a $N_2$ atmosphere. [b] Isolated yields were recorded above. [c] The diastereomer ratio was determined by $^1$H NMR.

(Scheme 1b, c). These results implied that the diastereoselectivity of the present cyclization could be controlled mostly by the C(4) substituent.[16]

The reaction of (*E*)-ethyl 6-bromo-3-methylhex-2-enoate (**1k**) with **2a** delivered cyclopentane **3ka** bearing two successive quaternary carbon centers (Scheme 2a). Intrigued by whether the protonation process after the conjugate addition

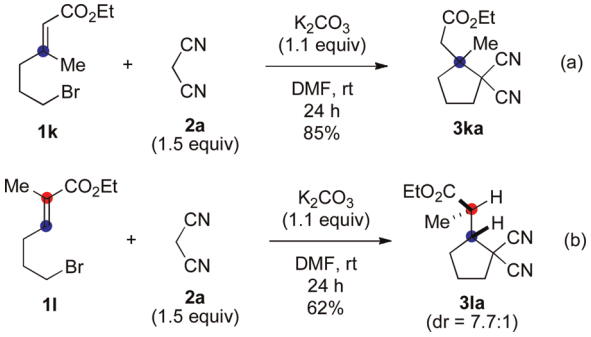
**Scheme 1.** Effects of the Position of Substituents




was selective,[17] (*E*)-ethyl 6-bromo-2-methylhex-2-enoate (**1l**) was subjected to the present reaction conditions with malononitrile (**2a**). The reaction afforded cyclopentane **3la** with good diastereoselectivity (7.7:1), where the (*R**, *R**)-isomer was formed as a major product probably via a concerted process of C−C bond formation and protonation (Scheme 2b; see Supporting Information for more details).[18]

Finally, further derivatization of the dicyanocyclopentanes and cyanophenylsulfonylcyclopentanes **3** was explored (Schemes 3 and 4). Dicyanocyclopentane **3aa** was treated with *n*-$Bu_3SnH$ in the presence of a catalytic

**Scheme 2.** Reactions of **1k** and **1l**




amount of AIBN, affording monodecyanated product **4aa**.[19] Chemoselective reduction of the ethoxycarbonyl

(16) The diastereoselectivity of the cyclized product **3** was confirmed by the X-ray crystallographic analysis of several compounds as well as the NOE analysis of the corresponding lactone derivatives in Schemes 3 and 4. See Supporting Information for more details.

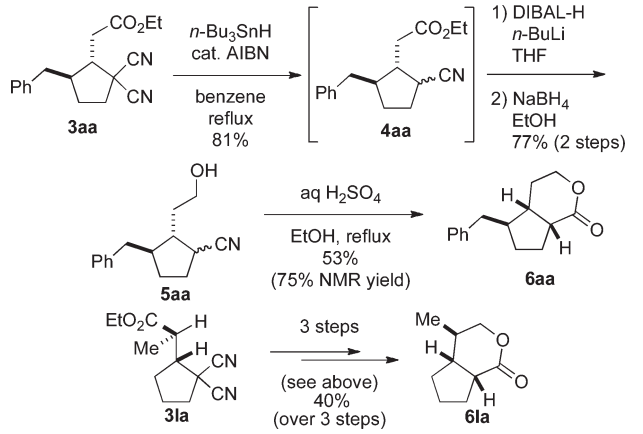
(17) For discussion of diastereoselective (enantioselective) protonation in conjugate addition of nucleophiles to acrylate derivatives, see: (a) Mohr, J. T.; Hong, A. Y.; Stoltz, B. M. *Nat. Chem.* **2009**, *1*, 359. (b) Duhamel, L.; Duhamel, P.; Plaquevent, J.-C. *Tetrahedron: Asymmetry* **2004**, *15*, 3653. (c) Niu, D.; Zhao, K. *J. Am. Chem. Soc.* **1999**, *121*, 2456.

(18) The stereochemistry of **3la** was determined by the NOE analysis of the corresponding lactone derivative **6la** prepared from **3la** via the procedures in Scheme 3.

(19) Curran, D. P.; Seong, C. M. *Synlett* **1991**, 107.

group of **4aa** by Kim's procedure[20] using the ate complex of DIBAL-H and *n*-BuLi gave alcohol **5aa**, which with aqueous acid treatment underwent lactonization, delivering *cis*-bicyclic lactone **6aa** in good yield (Scheme 3). The conversion of **3la** to lactone **6la** could lead to the confirmation of the stereochemical outcome by NOE measurement.

**Scheme 3.** Chemoselective Reduction–Lactonization of Dicyanocyclopentanes **3aa** and **3la**



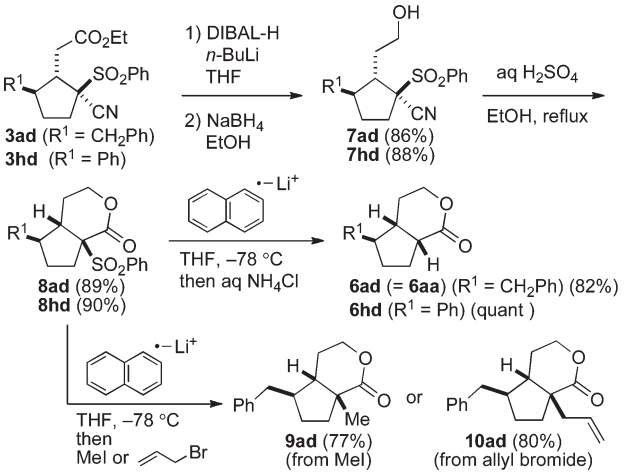

Kim's chemoselective reduction of the ethoxycarbonyl group of **3ad** and **3hd** followed by aqueous acid treatment gave α-sulfonyl bicyclic lactones **8ad** and **8hd**, respectively, in good yields. Reductive cleavage of the phenylsulfonyl group of **8** with lithium naphthalenide followed by protonation could afford *cis*-bicyclic lactone **6** smoothly with retention of the configuration. Similarly, the resulting lithium enolate generated from **8** could be trapped with carbon electrophiles such as methyl iodide and allyl bromide, giving **9ad** and **10ad** bearing a new quaternary carbon center with retention of the configuration.[21]

(20) Kim, S.; Ahn, K. H. *J. Org. Chem.* **1984**, *49*, 1217.

(21) The stereochemistry of **9ad** and **10ad** was determined by the NOE analysis, see Supporting Information.

(22) The preliminary discussion about the orign of the diastereoselectivity in the cyclization was described in Supporting Information.

**Scheme 4.** Chemoselective Reduction–Lactonization of Cyanophenylsulfonylcyclopentanes **3ad** and **3hd**




In summary, a concise and stereoselective methodology for the synthesis of highly substituted carbocycles has been developed.[22] Further investigation on the application of the present strategy to construct complex organic molecules is currently underway.

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**Supporting Information Available.** Experimental procedures, characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org. The authors declare no competing financial interest.

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