

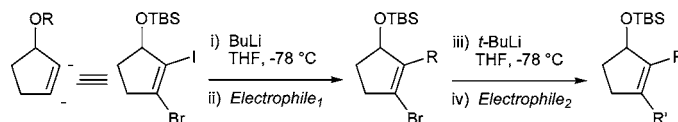
1,2-Bisanionic Coupling Approach to 2,3-Disubstituted Cyclopentenols and Cyclopentenones

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Received March 16, 2006

ABSTRACT

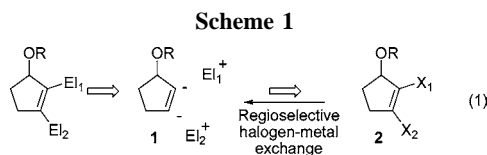


We describe a new approach to 2,3-disubstituted cyclopentenols and cyclopentenones through two consecutive regioselective additions of equal or different electrophiles to a cyclopentene bisanionic synthon. Indeed, on exposure to BuLi, 3-bromo-2-iodocyclopent-2-enol *O*-TBS ether undergoes iodine–lithium permutation with complete regioselectivity. Successive reaction of the monolithium anion with different C(sp²)- and C(sp³)-electrophiles affords the corresponding 2-substituted-3-bromocyclopentenol derivative. Subsequent bromo–lithium exchange with *t*-BuLi, followed by reaction with an equal or different electrophile, affords the desired 2,3-disubstituted cyclopentenol.

The 2,3-disubstituted cyclopentenol and cyclopentenone structural units are present in a wide range of useful synthetic intermediates and in a vast number of natural products endowed with a broad spectrum of biological activity.¹ Therefore, new methods of their construction are intensively searched.² With some notable exceptions,³ disubstituted cyclopentenones are built up from acyclic precursors.² In contrast, as shown in Scheme 1, we foresaw the possible

In principle, this novel strategy could be realized through two regioselective halogen–lithium permutations⁴ of a protected 2,3-dihalocyclopentenol **2**,⁵ each followed by reaction with an electrophile. Thus, a straightforward route to a great variety of disubstituted cyclopentenones appeared easily at hand, thanks to the ready preparation of dihalo-derivatives of type **2** (vide infra) and the well-known chemistry of organolithium compounds.⁶

At the onset of our work, the prospect of achieving this appealing dianionic synthon appeared, indeed, to be an uneasy task. In fact, regioselective monolithiation of unsymmetrically substituted halogenated compounds has been observed so far only for a handful of aromatic derivatives,⁷



assembly of such units through two consecutive regioselective additions of equal or different electrophiles to a cyclopentene bisanionic synthon **1**.

(1) Representative examples: (a) for prostaglandins, see: Straus, D. S.; Glass, C. K. *Med. Res. Rev.* **2001**, *21*, 185–210. (b) For jasmonates, see: Beale, M. H.; Ward, J. L. *Nat. Prod. Rep.* **1998**, 533–548. (c) For phytoprostanes, see: Thoma, I.; Krischke, M.; Loeffler, C.; Mueller, M. *J. Chem. Phys. Lipids* **2004**, *128*, 135–148. (d) For dicranenones, see: Sakai, K.; Fujimoto, T.; Yamashita, M.; Kondo, K. *Tetrahedron Lett.* **1985**, *26*, 2089–2092.

(2) (a) Gibson, S. E.; Lewis, S. E.; Mainolfi, N. *J. Organomet. Chem.* **2004**, *689*, 3873–3890. (b) Trost, B. M.; Pinkerton, A. B. *J. Org. Chem.* **2001**, *66*, 7714–7722 and references therein. (c) Frühauf, H.-W. *Chem. Rev.* **1997**, *97*, 523–596.

(3) See, for example: (a) Mikolajczyk, M.; Mikina, M.; Zurawinski, R. *Pure Appl. Chem.* **1999**, *71*, 473–480. (b) Pour, M.; Negishi, E.-i. *Tetrahedron Lett.* **1997**, *38*, 525–528. (c) Ho, T.-L. *Synth. Commun.* **1974**, *4*, 265–287.

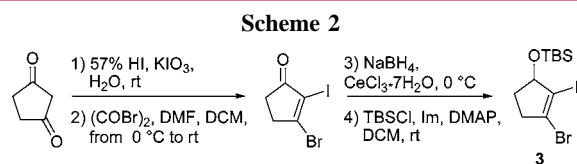
(4) Jones, R. G.; Gilman, H. In *Organic Reactions*; Adams, R., Ed.; Wiley: New York, 1951; Vol VI, pp 339–366.

(5) Introduction of a protecting group was necessary in light of the prospected reactions of **2** with aliphatic halides.

(6) (a) Chinchilla, R.; Nájera, C.; Yus, M. *Tetrahedron* **2005**, *61*, 3139–3176. (b) *The Chemistry of Organolithium Compounds*; Rappoport, Z.; Marek, I., Eds.; Wiley: New York, 2004.

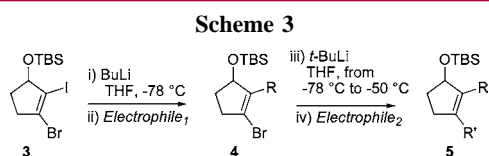
in particular when an ortho-orienting metalation group is present. In contrast, it has not yet been addressed to unsymmetrical alicyclic 1,2-dihaloolefins, even though examples of generation of 1-lithio-2-bromocyclopentenes from symmetrical dibromocyclopentenes, followed by alkylation, are in the literature.^{7a,8}

We focused our attention on the monolithiation of *O*-TBS-protected 2-iodo-3-bromocyclopentenol **3**,⁹ with the prospect of achieving a faster halogen/metal exchange at C-2 than at C-3 (Scheme 3). Our rationale was based on the higher



strength of the C–Br bond than the C–I bond¹⁰ and the higher reactivity of iodides than bromides in the exchange reaction.¹¹ Moreover, the combined electron-withdrawing effects of the oxygen and the bromine atoms on vicinal carbons were expected to stabilize a negative charge at C-2 better than at C-3.

To test our assumption, compound **3** was exposed to BuLi (1.1 equiv) at $-78\text{ }^{\circ}\text{C}$ in THF, and after 10 min, the resulting yellowish anion was quenched by the addition of saturated aqueous NH_4Cl at the same temperature. GC-MS analysis of the reaction mixture revealed a complete conversion of **3** into one monobromo derivative, which was isolated in 88% yield and assigned as structure **4a** (Scheme 3, R = H in



formula **4**) by NMR COSY and NOESY experiments.

This result demonstrated that, on exposure to BuLi, dihalocyclopentenol **3** underwent a single and efficient halogen–lithium permutation, the iodine atom at C-2 being

(7) (a) Schlosser, M. In *Organometallics in Synthesis: A Manual*; Schlosser, M., Ed.; Wiley: New York, 2002; pp 101–137. (b) Liu, Y.; Gribble, G. W. *Tetrahedron Lett.* **2002**, *43*, 7135–7137.

(8) (a) Foubelo, F.; Yus, M. *Curr. Org. Chem.* **2005**, *9*, 459–490. (b) Dastan, A.; Uzundumlu, E.; Balci, M.; Fabris, F.; De Lucchi, O. *Eur. J. Org. Chem.* **2004**, 183–192. (c) Tranmer, G. K.; Yip, C.; Handerson, S.; Jordan, R. W.; Tam, W. *Can. J. Chem.* **2000**, *78*, 527–535. (d) Paquette, L. A.; Doyon, J. *J. Am. Chem. Soc.* **1995**, *117*, 6799–6800. (e) Gassman, P. G.; Gennick, I. *J. Am. Chem. Soc.* **1980**, *102*, 6863–6864.

(9) Easily available in four steps from commercial 1,3-cyclopentanedione, as depicted in Scheme 2.

(10) Vedeneyev, V. I.; Gurchich, L. V.; Kondrat'yev, V. N.; Medvedev, V. A.; Fraukevich, Y. L. *Bond Energies, Ionization Potentials and Electron Affinities*; E. Arnold: London, 1966.

(11) Gilman, H.; Langham, W.; Moore, F. W. *J. Am. Chem. Soc.* **1940**, *62*, 2327–2335.

exchanged with complete regioselectivity. To complete our test reactions, the bromocyclopentene **4a** (Scheme 3, R = H in formula **4**) was subsequently exposed to *t*-BuLi (2.5 equiv) at $-78\text{ }^{\circ}\text{C}$, followed by protonation (NH_4Cl) of the resulting anion, affording, uneventfully, the volatile debrominated cyclopentene **5a** (Scheme 3, R = R' = H in formula **5**) in 72% yield.

Subsequently, with the aim to extend this new methodology to the construction of mono- and disubstituted cyclopentenes, we tested different $\text{C}(\text{sp}^2)$ - and $\text{C}(\text{sp}^3)$ -electrophiles for quenching the vinyl anions produced from compound **3** (Scheme 3). Our results are summarized in Tables 1 and 2.

Table 1. Electrophilic Additions to 2-Monolithium Species Generated Regioselectively from Cyclopentene **3***

entry	electrophile	product	R	yield (%)
1	H^+	4a	H	88
2	CH_3CHO	4b^d	OH	92
3 ^a	$\text{CH}_3\text{CH}_2\text{CHO}$	4c^d	OH	95
4 ^a		4d^d	OH	95
5		4e	OH	48
6 ^a	CH_3I	4f	H_3C	91
7 ^b		4g		53
8		4h		67
9		4i		86
10 ^c		4j		77
11 ^c		4k		68

* General procedure: (i) 1.6 M BuLi (1.1 equiv), THF, $-78\text{ }^{\circ}\text{C}$, 12 min; (ii) electrophile (1.2 equiv), from $-78\text{ }^{\circ}\text{C}$ to $-30\text{ }^{\circ}\text{C}$ over 4 h. ^a General procedure, except that the reaction was quenched after 1 h at $-78\text{ }^{\circ}\text{C}$ (warming to $-30\text{ }^{\circ}\text{C}$ was not necessary). ^b General procedure, except that HMPA (6 equiv, *CAUTION: toxic!*) was added before adding the electrophile. ^c General procedure, except that 0.25 M lithium 2-thienylcyclopentene (1.1 equiv) in THF, $-78\text{ }^{\circ}\text{C}$, 20 min, was added before adding the electrophile. ^d Mixture of diastereomers.

The expected mono- (**4b–k**) and dialkylated (**5b–n**) products were obtained from compound **3** with complete regioselectivity and in satisfactory overall yields. To confirm the site selectivity of the first halogen–lithium exchange, compounds **5b–n** were produced in two separate steps, with isolation and structure determination of the corresponding intermediates of general formula **4**.

In principle, sequential replacement of halogens by electrophiles could be achieved in a one-pot operation; however, the overall efficiency was lower. Thus, treatment of **3** with BuLi (1.1 equiv), followed by propanal, afforded **4c** as a lithium alkoxide, which, without isolation, was exposed to *t*-BuLi (3.3 equiv), followed by acetaldehyde, to afford **5e** in 50% yield, as compared to 70% for the two-step procedure.

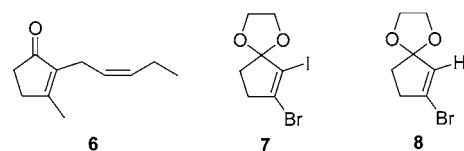
Table 2. Electrophilic Additions to Lithium Species Generated from Bromides 4*

entry	bromide	electrophile	product	R'	yield (%)
1	4a	H ⁺	5a	H-	72
2 ^a	4b	CH ₃ CHO	5b ^c		69
3 ^a	4b	CH ₃ CH ₂ CHO	5c ^c		72
4 ^a	4b	PhCHO	5d ^c		72
5 ^a	4c	CH ₃ CHO	5e ^c		85
6 ^a	4c	CH ₃ CH ₂ CHO	5f ^c		76
7 ^a	4d	CH ₃ CHO	5g ^c		76
8 ^a	4e		5h		45
9	4f		5i ^c		78
10	4f	CH ₃ I	5j	H ₃ C-	78
11 ^b	4f		5k		65
12	4i		5l ^c		61
13	4i	CH ₃ I	5m	H ₃ C-	73
14 ^b	4i		5n		48

* General procedure: (i) 2.7 M *t*-BuLi (2.5 equiv), THF, -78 °C, 30 min, followed by an increase of the temperature to -50 °C in 30 min; (ii) electrophile (1.2 equiv), -78 °C → -20 °C over 5 h. ^a General procedure, except that NaH (1.1 equiv), 0 °C, 10 min, was added before the addition of *t*-BuLi (3.3 equiv) at -78 °C. ^b General procedure, except that HMPA (6 equiv, *CAUTION: toxic!*) was added immediately before the addition of the electrophile. ^c Mixture of diastereomers.

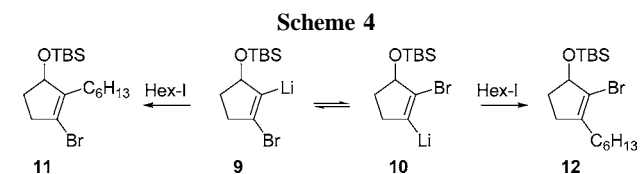
In general, reactions with C(sp³)-electrophiles (Table 1, entries 6–11; Table 2, entries 10, 11, 13, 14) gave lower yields than those with carbonyl compounds (Table 1, entries 2–5; Table 2, entries 2–9, 12) and certain electrophiles required the general experimental procedure to be slightly modified (see footnotes to Tables 1 and 2). Thus, either the addition of HMPA as a cosolvent (Table 1, entry 7; Table 2, entries 11, 14) or the preparation of a mixed organocuprate species (Table 1, entries 10, 11) was required before electrophile addition.

Compounds **5b–n** can be considered direct precursors of 2,3-disubstituted cyclopentenones, according to a well-established chemistry. As a representative example, cyclopentene **5m** (Table 2, entry 13) was readily converted¹² into the well-known *cis*-jasmone **6**.^{1b} In this context, to have more direct access to disubstituted cyclopentenones, we tried to extend our methodology to acetal **7**; however, the preparation of **7** from the corresponding ketone, under different acetalization conditions,¹³ was not a clean reaction and resulted in some substrate decomposition. Indeed, unsuccessful ketalization of 3-bromocyclopentenones has been observed also by other authors.¹⁴ Therefore, we abandoned this approach, even if acetal **7** on exposure to BuLi at -78 °C in THF, followed by protonation, gave the bromo derivative **8** in 75% yield with complete regioselectivity.



An interesting observation was made about the structural integrity of the 3-bromo-2-lithio anion **9**, obtained from **3** by iodine exchange with BuLi (1.1 equiv) in THF at -78 °C. In an attempt to accelerate the alkylation step by 1-iodohexane (1.1 equiv), a solution of **9**, to which the alkyl iodide and DMPU (5 equiv) had been added, was brought to 0 °C and left at this temperature for 5 h.

Chromatographic separation of the products afforded, in an almost 1:1 ratio and 68% combined yields, the two regioisomeric 2- and 3-hexyl derivatives, **11** and **12**, respectively, containing a bromine atom (MS) on carbons 3 and 2, respectively. The formation of these compounds can likely be explained by a bromine positional scramble, whose mechanism has not yet been established, with isomerization of **9** to 2-bromo-3-lithiocyclopentene **10**, followed by alkylation of the two lithium regioisomers (Scheme 4). 1,2-



Positional permutations of the lithium and bromine atoms have been well studied for carbo- and heterocyclic aromatic compounds,^{7a,15} but it appears to be an unprecedented process for aliphatic compounds.

(12) (i) 1 M TBAF (2 equiv), THF, room temperature; (ii) MnO₂ (30 equiv), pentane, 5 h, room temperature; 85% overall yield.

(13) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Wiley: New York, 1999.

(14) Shih, C.; Swenton, J. S. *J. Org. Chem.* **1982**, *47*, 2825–2832.

(15) Mongin, F.; Desponds, O.; Schlosser, M. *Tetrahedron Lett.* **1996**, *37*, 2767–2770 and references therein.

In conclusion, we have demonstrated that, under optimal experimental conditions, the dihalocyclopentenol **3** can be considered as a synthetic equivalent of the 2,3-bisanionic synthon **1**. We stress the simplicity with which the two consecutive regioselective halogen/metal permutations can be executed and the variety of electrophiles which can be added to the corresponding vinyl anions. Thus, this approach to different 2,3-disubstituted cyclopentenols compares quite favorably to the existing methods. Moreover, in addition to their oxidation to cyclopentenones, cyclopentenols are useful intermediates for a number of other synthetic transformations

(16) In contrast to 1-lithio-2-bromocyclopentene which is relatively stable up to 25 °C, 1-lithio-2-bromocyclohexene is reported to lose LiBr even at ≤ 120 °C, hampering the extension of this methodology to 1,2-dihalocyclohexenes.

(17) For studies on the stability of different 1-lithio-2-halocycloalkenes, see: (a) Wittig, G.; Mayer, U. *Chem. Ber.* **1963**, *96*, 329–341. (b) Wittig, G.; Mayer, U. *Chem. Ber.* **1963**, *96*, 342–348. (c) Wittig, G.; Weinlich, J.; Wilson, E. R. *Chem. Ber.* **1965**, *98*, 458–470.

such as Claisen rearrangements, allylic couplings, allylic transposition of the OH group, as well as simple hydrogenation to cyclopentanols. Thus, we believe that this new 1,2-bisanionic coupling methodology can afford a general and straightforward approach to a diverse range of five-membered ring targets.^{16,17}

Acknowledgment. This research was supported by Italian MIUR (funds COFIN and FIRB). We thank Prof. Mariella Mella and Prof. Giorgio Mellerio for recording NMR and MS spectra, respectively.

Supporting Information Available: General experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL060654Y