ORGANIC LETTERS

2007
Vol. 9, No. 15
2823−2826

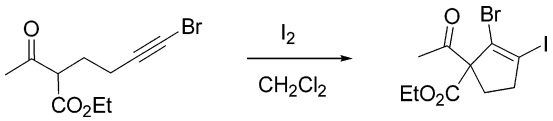
Iodocarbocyclization Reaction of β-Ketoesters and Alkynes

José Barluenga,* David Palomas, Eduardo Rubio, and José M. González

Instituto Universitario de Química Organometálica "Enrique Moles"-Unidad Asociada al CSIC, Universidad de Oviedo, Oviedo 33071, Spain
barluenga@uniovi.es

Received May 4, 2007

ABSTRACT



Iodocyclopentenes are formed at room temperature upon straight reaction of δ-alkynyl-β-ketoesters with I_2 for several hours. Cyclizations involving terminal and substituted (alkyl, aryl, Br, I) alkynes were accessed. Twelve examples with yields ranging from 20% up to 80% are reported (out of them eight cases are above 60%). These results present the first examples of the iodonium-promoted 5-*endo-dig* carbocyclization of active methyne substrates onto alkynes.

The metal-catalyzed addition reaction of α-to-carbonyl C−H bonds toward unactivated alkynes (Figure 1a)[1] and related reactions of preformed enolates or active systems[2] furnish valuable synthetic intermediates and are part of more complex preparative sequences.[3]

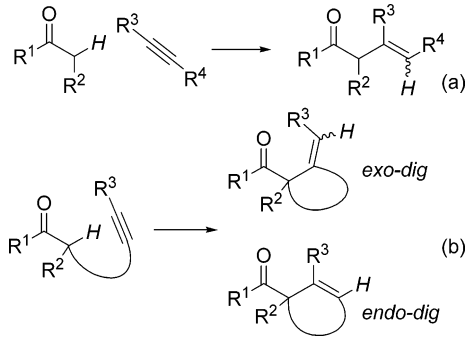


Figure 1. Inter- and intramolecular addition of an activated C−H bond to an unactivated alkyne.

The Conia-ene reaction is an intramolecular version of this process that was originally accomplished at rather high temperature (Figure 1b).[4] The cyclization takes place following an *exo-dig* mode and partial isomerization of the alkene is observed in the final product. Metal-catalyzed reactions have been developed to approach this cycloisomerization under milder conditions. Selective *exo-dig* ring-closure from ϵ-alkynyl-β-ketoesters and related malonate derivatives have often been observed.[5] However, the 5-*endo*-cyclization of δ-alkynyl-substituted β-ketoesters[6] or from the related 6-sililoxy-5-en-1-ynes[7] furnishing cyclopentene derivatives has been less frequently reported. Moreover, cyclizations leading to substituted indenes were accomplished via palladium-catalyzed 5-*endo* carbocyclization reactions of malonates and related anions onto aryl tethered internal alkynes.[8] A related approach from 2-(*o*-iodophenyl)malonates and alkynes was developed.[8b,9]

(1) (a) Endo, K.; Hatakeyama, T.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **2007**, *129*, 5264−5271. (b) Kuninobu, Y.; Kawata, A.; Takai, K. *Org. Lett.* **2005**, *7*, 4823−4825. (c) Nakamura, M.; Endo, K.; Nakamura, E. *Org. Lett.* **2005**, *7*, 3279−3281. (d) Nakamura, M.; Endo, K.; Nakamura *J. Am. Chem. Soc.* **2003**, *125*, 13002−13003. For a related transformation, see also: (e) Nishimura, Y.; Ameniya, R.; Yamaguchi, M. *Tetrahedron Lett.* **2006**, *47*, 1839−1843.

(2) (a) Nakamura, M.; Fujimoto, T.; Endo, K.; Nakamura, E. *Org. Lett.* **2004**, *6*, 4837−4840. (b) Nakamura, M.; Liang, C.; Nakamura, E. *Org. Lett.* **2004**, *6*, 2015−2017. (c) Ameniya, R.; Fujii, A.; Arisawa, M.; Yamaguchi, M. *J. Organomet. Chem.* **2003**, *686*, 94−100. (d) Arisawa, M.; Ameniya, R.; Yamaguchi, M. *Org. Lett.* **2002**, *4*, 2209−2211. (e) Miura, K.; Saito, H.; Fujisawa, N.; Wang, D.; Nishikori, H.; Hosomi, A. *Org. Lett.* **2001**, *3*, 4055−4057. (f) Yamaguchi, M.; Hayashi, A.; Hirama, M. *J. Am. Chem. Soc.* **1993**, *115*, 3362−3363.

(3) (a) Li, Y.; Lu, Z.; Alper, H. *Org. Lett.* **2007**, *9*, 1647−1649. (b) Kuninobu, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2006**, *128*, 11368−11369. (c) Ochiai, M.; Ito, T.; Takaoka, Y.; Masaki, Y.; Kunishima, M.; Tani, S.; Nagao, Y. *J. Chem. Soc., Chem. Commun.* **1990**, 118−119. (d) Ochia, M.; Kunishima, M.; Nagao, Y.; Fuji, K.; Shiro, M.; Fujita, E. *J. Am. Chem. Soc.* **1986**, *108*, 8281−8283.

10.1021/ol0710459 CCC: $37.00
Published on Web 06/22/2007

Interestingly, Taguchi and Kitagawa established early that iodonium-triggered reactions are of practical interest to assemble the related (*E*)-2-iodomethylenecyclopentane scaffold by promoting the carbocyclization of a titanium enolate onto the alkyne (Figure 2a).[10,11] They expand the scope of

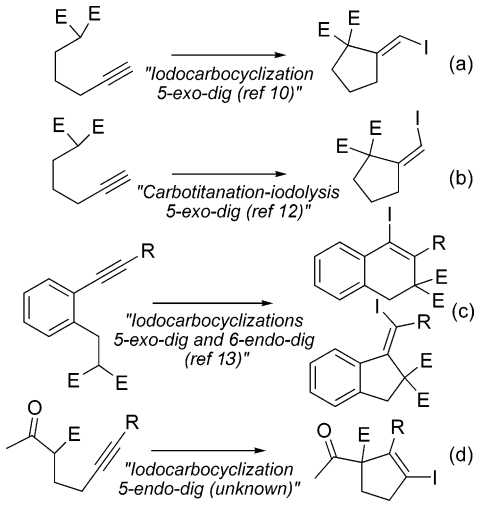


Figure 2. Products (E: CO_2R) arising from iodocarbocyclization reactions of ϵ-alkynylmalonate enolates (entries a,c) and from an alternative carbotitanation−iodolysis sequence (entry b). Target transformation (entry d).

the cyclization showing that an alternative carbotitanation of the alkyne followed by iodolysis of the resulting C−Ti bond renders the (*Z*)-isomers (Figure 2b).[12]

Recently, Liang used an iodination reaction in the presence of *t*-BuOK to accomplish the cyclization of 2-(2-ethynyl)-benzylmalonate derivatives and related methyne active compounds (Figure 2c).[13] The observed 5-*exo*- and 6-*endo-dig* selectivities were shown to be dependent on the starting material. On this basis, our interest[14] in iodination reactions with concomitant ring-elaboration[15] prompted us to investigate the challenging iodocarbocyclization reaction of an alkyne and an active methyne compound according to the more elusive 5-*endo-dig* mode,[16,17] as depicted in Figure 2 (entry d). The feasibility of this entry to cyclopentene derivatives is established herein.

Initially, different conditions were screened to attempt the target iodocarbocyclization of 2-acetylhept-5-ynoic acid ethyl ester **1a** to 1-acetyl-3-iodo-2-methylcyclopent-2-enecarboxylic acid ethyl ester **2a** (see Table 1). Reactions were conducted at room temperature, and I_2 and IPy_2BF_4 were assayed as potential iodinating trigger reagents (1:1 with respect to **1a**). The former gave simpler reaction crudes and offered better performance for the cyclization. Toluene, MeCN, and CH_2Cl_2 were tested as solvents, the latter allowing the cyclization to occur adequately. The major competing reaction pathway was the 1,2-addition of I_2 across the alkyne.[18] Its impact was minimized by increasing the dilution from initial 0.3 up to 0.05 M. With use of these simple experimental conditions, pure **2a** was isolated in 70% yield after reaction for 5 h and chromatographic purification (Table 1, entry 1).[19]

The effect of different additives over the outcome of the reaction in CH_2Cl_2 was investigated. Addition of $NaHCO_3$ increases the ratio in favor of the iodine 1,2-addition product,

(4) Conia, J. M.; Le Perchec, P. *Synthesis* **1975**, 1−19.

(5) (a) Pérez-Hernández, N.; Febles, M.; Pérez, C.; Pérez, R.; Rodríguez, M. L.; Foces-Foces, C.; Martín, J. D. *J. Org. Chem.* **2006**, *71*, 1139−1151. (b) Ochida, A.; Ito, H.; Sawamura, M. *J. Am. Chem. Soc.* **2006**, *128*, 16486−16487. (c) Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 17168−17169. (d) Gao, Q.; Zheng. B.-F.; Li, J.-H.; Yang, D. *Org. Lett.* **2005**, *7*, 2185−2187. (e) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526−4527. (f) Kitagawa, O.; Fujiwara, H.; Suzuki, T.; Taguchi, T.; Shiro, M. *J. Org. Chem.* **2000**, *65*, 6819−6825. (g) Renaud, J.-L.; Aubert, C.; Malacria, M. *Tetrahedron* **1999**, *55*, 5113−5128. (h) Bouyssi, D.; Monteiro, N.; Balme, G. *Tetrahedron Lett.* **1999**, *40*, 1297−1300. (i) Cruciani, P.; Stammler, R.; Aubert, C.; Malacria, M. *J. Org. Chem.* **1996**, *61*, 2699−2708. (j) Boaventura, M. A.; Drouin, J.; Conia, J. M. *Synthesis* **1983**, 801−804.

(6) (a) Staben, S. T.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 5350−5352. (b) McDonald, F. E.; Olson, T. C. *Tetrahedron Lett.* **1997**, *38*, 7691−7692.

(7) Iwasaba, N.; Miura, T.; Kiyota, K.; Kusama, H.; Lee, K.; Lee, P. H. *Org. Lett.* **2002**, *4*, 4463−4466.

(8) (a) Li, Y.; Yu, Z.; Alper, H. *Org. Lett.* **2007**, *9*, 1647−1649. (b) Guo, L.-N.; Duan, X.-H.; Bi, H.-P.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem.* **2007**, *72*, 1538−1540. (c) Zhang, D.; Liu, Z.; Yum, E.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 251−262. (d) Duan, X.-H.; Guo, L.-N.; Bi, H.-P.; Liu, X.-Y.; Liang, Y.-M. *Org. Lett.* **2006**, *8*, 3053−3056. (e) Guo, L.-N.; Duan, X.-H.; Bi, H.-P.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem.* **2006**, *71*, 3325−3327.

(9) Zhang, D.; Yum, E. K.; Liu, Z.; Larock, R. C. *Org. Lett.* **2005**, *7*, 4963−4966.

(10) Kitagawa, O.; Inoue, T.; Hirano, K.; Taguchi, T. *J. Org. Chem.* **1993**, *58*, 3106−3112.

(11) Related cyclizations were described for *N*-alkyl-*N*-propargyl-β-ketoamides using alternative conditions: (a) Cossy, J.; Thellend, A. *Tetrahedron Lett.* **1990**, *31*, 1427−1428. Some examples of related 5-*exo-dig* radical cyclizations by atom-transfer reactions of 2-iodo-6-alkynyl esters have been reported: (c) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140−3157.

(12) (a) Kitagawa, O.; Suzuki, T.; Inoue, T.; Taguchi, T. *Tetrahedron Lett.* **1998**, *39*, 7357−730. (b) Kitagawa, O.; Suzuki, T.; Inoue, T.; Watanabe, Y.; Taguchi, T. *J. Org. Chem.* **1998**, *63*, 9470−9475. For an account on their work on iodocarbocyclization and iodoaminocyclization reactions see: (c) Kitagawa, O.; Taguchi, T. *Synlett* **1999**, 1191−1199.

(13) Bi, H.-P.; Guo, L.-N.; Duan, X.-H.; Gou, F.-R.; Huang, S.-H.; Liu, X.-Y.; Liang, Y.-M. *Org. Lett.* **2007**, *9*, 397−400.

(14) Recent work: (a) Barluenga, J.; Vázquez-Villa, H.; Merino, I.; Ballesteros, A.; González, J. M. *Chem. Eur. J.* **2006**, *12*, 5790−5805. (b) Barluenga, J.; Trincado, M.; Rubio, E.; González, J. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 3140−3143.

(15) Representative recent work: Worlikar, S. A.; Kesharwani, T.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 1347−1350. (b) Amjad, M.; Knight, D. W. *Tetrahedron Lett.* **2006**, *47*, 2825−2828. (c) Zhou, C.; Dubrovsky, A. V.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 1626−1632. (d) Hessian, K. O.; Flynn, B. L. *Org. Lett.* **2006**, *8*, 243−246.

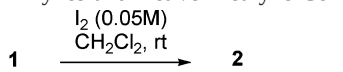
(16) Recent iodination reactions with ring elaboration: (a) Foot, O. F.; Knight, D. W.; Low, A. C. L.; Li, Y. F. *Tetrahedron Lett.* **2007**, *48*, 647−650. (b) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 10292−10296. Early work: (c) Bew, S. P.; Knight, D. W. *Chem. Commun.* **1996**, 1007−1008.

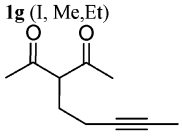
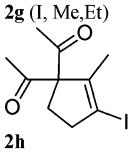
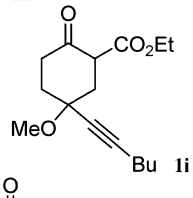
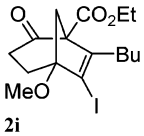
(17) Related metal-catalyzed 5-*endo-dig* alkyne carbocyclization by reaction with the CH bond: (a) Ajamian, A.; Gleason, J. L. *Org. Lett.* **2003**, *5*, 2409−2411. (b) Tanaka, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 11492−11493. Ketones: (c) Kel'in, A. V.; Gevorgyan, V. *J. Org. Chem.* **2002**, *67*, 95−98. With imines: (d) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074−2075. See also: (e) Smith, C. R.; Bunnelle, E. M.; Rhodes, A. J.; Sarpong, R- *Org. Lett.* **2007**, *9*, 1169−1171.

(18) Addition of I_2 to alkynes: (a) Larson, S.; Luidhardt, T.; Kabalka, G. W.; Pagni, R. M. *Tetrahedron Lett.* **1988**, *29*, 35−36. (b) Hollins, R. A.; Campos, M. P. A. *J. Org. Chem.* **1979**, *44*, 3931−3934. See also: (c) Hénaff, N.; Stewart, S. K.; Whiting, A. *Tetrahedron Lett.* **1997**, *38*, 4525−4526.

(19) All new compounds gave NMR spectroscopic and analytical or MS data in agreement with their proposed structures. For further details see the Supporting Information.

Table 1. Iodonium-Promoted 5-*endo-dig* Mode Carbocyclization of Alkynes and Active Methyne Compounds[a]



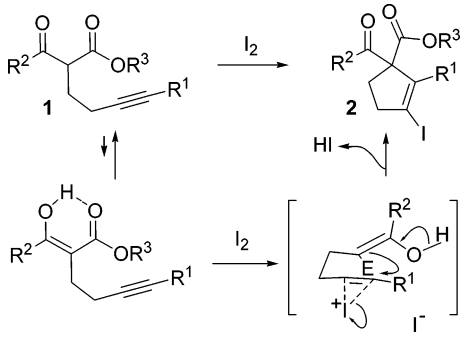
entry	substrate **1** (R^1, R^2, R^3)	time	product **2** (R^1, R^2, R^3)	isolated yield (%)
1	**1a** (Me, Me, Et)	5 h	**2a** (Me, Me, Et)	70
2	**1b** (Me, Me, Bn)	5 h	**2b** (Me, Me, Bn)	60
3	**1c** (Me, Ph, Et)	24 h	**2c** (Me, Ph, Et)	20
4	**1d** (Et, Me, Et)	8 h	**2d** (Et, Me,Et)	67
5	**1e** (Ph, Me,Et)	8 h	**2e** (Ph, Me,Et)	50
6	**1f** (Br, Me,Et)	5 d	**2f** (Br, Me,Et)	75
7	**1g** (I, Me,Et)	6 h	**2g** (I, Me,Et)	57
8	 **1h**	48 h	 **2h**	62
9	 **1i**	15 h	 **2i**	62
10	**1j** (H)	7 d	**2j** (H)	20[b]
11	**1k** (Ph)	4 h	**2k** (Ph)	60
12	**1l** (I)	24 h	**2l** (I)	80

[a] I_2 was added to a solution of the corresponding δ-alkynyl-β-ketoester in CH_2Cl_2 and then stirring was prolonged for the given time, until TLC showed the consumption of **1**. [b] Using 0.025 M solution.

whereas *i*-Pr_2NEt or DBU inhibit the reactions. So, addition of bases was found to be detrimental for the desired transformation. Conversely, when the cyclization was conducted under the influence of added sulfuric acid (up to 0.5 equiv) the reaction outcome was quite similar to that without added acid. Furthermore, different metal salts were tested without showing major impact over the cyclization. Thus, we further investigated the scope of this novel cyclization using the above-described conditions for obtaining **2a** as the standard protocol (see Table 1). Both β-ketoester and 1,3-diketone derivatives (entry 8) enter as substrates in this process. Internal alkynes wih alkyl and aryl substituents (entries 5 and 11) were cyclized with this protocol. The formation of bicyclic skeletons is also possible (entry 9). Though in modest yield, a terminal alkyne also gave some alkyaltion product (**1j**, entry 10), in this case addition of I_2 across the alkyne represents the main reaction path. The process works nicely when haloalkynes (entries 6, 7, and 12) were exposed to the action of iodine, resulting in the formation of doubly halogenated alkenes with potential for further synthetic elaboration at both sp^2 carbon atoms. This class of compounds was not previously reported in alternative 5-*endo-dig* approaches.

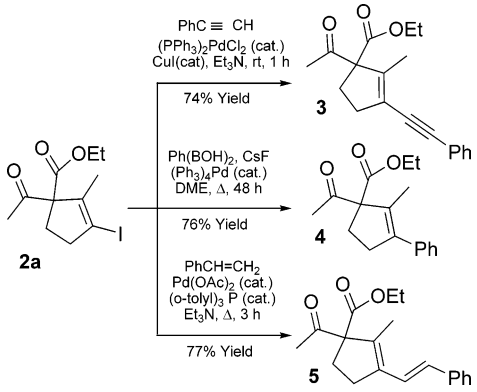
A tentative mechanistic interpretation to justify the formation of products **2** might reasonably assume an attack of the enol tautomer from **1** to the intermediate ion[20] resulting in electrophilic activation of the alkyne[21] (Scheme 1).

Scheme 1. Proposed Mechanistic Pathway To Account for the Formation of Carbocycles **2** from δ-Alkynyl-β-ketoesters **1**



The process reported herein allows the synthesis of tetrasubstituted alkenes by exploiting the reactivity of the C−I bond to introduce molecular diversity using subsequent metal-catalyzed cross-coupling reaction steps.[22] Several representative examples show the synthetic utility of the iodocarbocyclization/cross-coupling tandem sequence for the conversion of **1a** into different types of C-substituted derivatives, and are summarized in Scheme 2. Also of interest, as expected, the Sonogashira cross-coupling reaction of **2f** with phenylacetylene takes place smoothly at the C−I bond with total chemoselectivity to furnish a bromine-containing carbocycle[23] that then can be further elaborated by using the remaining C−Br bond.

Scheme 2. Tetrasubstituted Alkenes upon Novel Tandem Sequence: Iodocarbocyclization/Cross-Coupling from δ-Alkynyl-β-ketoesters



(20) Recent theoretical work on halovinyl and bridged halonium ions: Okazi, T.; Laali, K. K. *J. Org. Chem.* **2006**, *71*, 9643−9650.

Overall a straightforward access to accomplish the 5-*endo-dig* mode carbocyclization of active methyne compounds onto alkynes (internal and terminal) has been executed. This process nicely complements the 5-*exo-dig* regioselectivity noticed early in related iodonium-promoted carbocyclization reactions for preformed titanium enolates and parallels the regiocontrol outcome recently reported in several metal-catalyzed cyclization reactions for the same starting materials.

Acknowledgment. This research was partially supported by the Spanish DGI (CTQ2004-08077-C02-01) and the Consejería de Cultura del Principado de Asturias (IB05-136) D.P. wants to thank the Spanish MEC for a fellowship.

Supporting Information Available: Experimental procedures, characterization data, ^{1}H and ^{13}C spectra for compounds **1**−**5**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0710459

(21) A radical pathway may also be considered. We conducted the room temperature cyclization of **1a**, reaction with I_2 in CH_2Cl_2, in the presence of the radical inhibitor BHT. The reaction time for the consumption of **1a** was the same and **2a** was formed in comparable yield. On this basis, we invoke an ionic reaction path.

(22) *Metal Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004.

(23) 1-Acetyl-2-bromo-3-phenylethynylcyclopent-2-ene carboxylic acid ethyl ester **6** was isolated in 89% yield after reaction of **2f** with phenylacetylene (1.1 equiv) and $(PPh_3)_2PdCl_2$-CuI (5 mol %) in Et_3N at rt, for 1 h.