Tetrahedron Letters, Vol. 35, No. 1, pp. 23-26, 1994
Printed in Great Britain

0040-4039/94 $6.00 + .00
Pergamon Press Ltd

Preparation of Bis-Cyclopentene Ring Systems via Reaction of Bis[phenyl(iodonium)] Diyne Triflates with Soft Nucleophiles

Rik R. Tykwinski, Peter J. Stang,* and Neal E. Persky

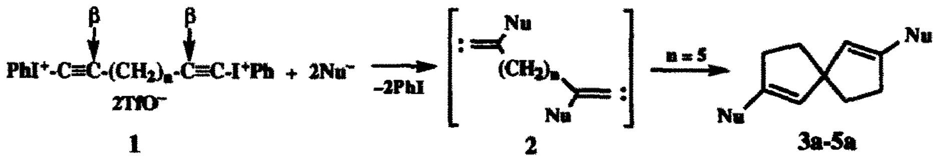
Department of Chemistry, University of Utah, Salt Lake City, UT 84112

Abstract: *The synthesis and characterization of substituted bis-cyclopentene ring systems derived from the interaction of nucleophiles and bis[phenyl(iodonium)] diyne triflate salts is described.*

The formation of cyclic products from acyclic precursors represents a fundamental challenge of organic synthesis. Furthermore, since many natural products and biologically active compounds contain multiple rings, methods affording bicyclic products via tandem cyclizations of acyclic precursors are of particular, general interest. The present paper reports the formation of a variety of bis-cyclopentene ring systems in good yields, under mild conditions, via the reaction of bis[phenyl(iodonium)] diyne triflates[1] with "soft" anionic nucleophiles.[2]

Although a number of electrophilic sites are present within alkynyl iodonium salts,[3] addition of nucleophiles to the electron deficient β acetylenic carbon (eq. 1) is generally favored.[4] In reactions involving nucleophiles of low migratory aptitude, 1,5-C–H bond insertion of the alkylidenecarbene intermediate,[5] **2**, results in predominant formation of cyclopentene products, rather than rearrangement to the functionalized acetylene.

Equation 1 outlines the pathway for the reaction of nucleophiles with bis(iodonium) diyne triflates **1a-c**.

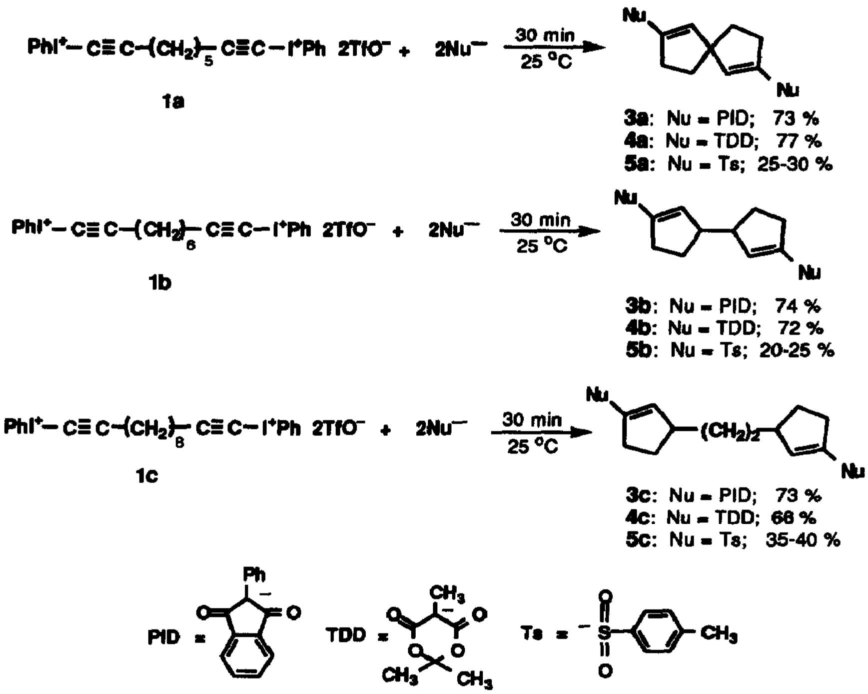


(1)

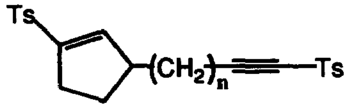
Following Michael addition of the nucleophile to the β acetylenic carbon, subsequent loss of iodobenzene yields the bis-alkylidenecarbene **2**. The intermediate carbene then undergoes dual 1,5-intramolecular C–H insertions affording the substituted bis-cyclopentene products.

The respective iodonium salt, **1a-c**, was added to a THF solution of potassium 2-phenyl-1,3-indanedionate (PID) or potassium 2,2,5-trimethyl-1,3-dioxane-4,6-dionate (TDD) (deprotonation with KO^{t}Bu in THF at 25 °C) and allowed to react for 30 minutes at room temperature. Following removal of NaOTf, the desired bis-cyclopentene products are easily isolated in high yields, as stable solids, via crystallization by the addition of ether and hexanes to a CH_2Cl_2 solution of the reaction mixture, followed by refrigeration.[6] This method affords either the substituted spiro-fused products **3a-5a** or the tethered cyclopentene systems **3b-5b** and **3c-5c** (Scheme I), depending upon the number of methylene units separating the two alkynyliodonium moieties. All products have been characterized by IR, ^{1}H NMR, ^{13}C NMR and EA or HRMS. Compounds **4b** and **3c-4c** were isolated and characterized as 1:1 mixtures of diastereomers, whereas pure samples of the diastereomers of **3b** were separated by fractional crystallization and independently characterized.

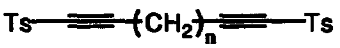
Scheme I



The reaction of **1a-c** with NaTs (Ts = p-$CH_3C_6H_4SO_2$) was found to give a mixture of the desired bis-cyclized product (20-40 % isolated yields), monocyclized alkynyl sulfones **6**, and small amounts of the bis-sulfonyl diynes **7**. Formation of this mixture via rearrangement or insertion was investigated by conducting the reaction under a variety of conditions,[7-9] the results of which are tabulated in Table 1. As predicted by previous studies of alkylidenecarbene C–H bond insertions,[10] reactions conducted at lower temperatures and in solvents with higher dielectric constants gave the highest ratio of bis-cyclized/monocyclized products. The respective cyclizations were also attempted in THF, t-BuOH, MeOH, glyme and CH_3CN, at several temperatures and concentrations. Analysis of these reactions, however, showed the formation of a complex mixture of products which were inseparable.



6a: n = 2
b: n = 3
c: n = 5



7a: n = 5
b: n = 6
c: n = 8

Table 1. Product Ratios[a] of **5a**:**6a**:**7a** and **5b**:**6b**:**7b** from Reaction of **1a-b** with Sodium *p*-Toluene Sulfinate.

Conditions	Ratio, %			yield,[b]	Ratio, %			yield,[b]
	5a	**6a**	**7a**	%	**5b**	**6b**	**7b**	%
benzene, 25 °C	36	54	10	94	41	54	5	87
CH_2Cl_2, 25 °C	41	54	5	88	46	53	~ 1	94
CH_2Cl_2, -43 °C	48	49	3	74	53	46	~ 1	82
CH_2Cl_2/H_2O	46	48	6	84	55	41	4	75

[a]Determined by ^1H NMR. [b]Combined, isolated yield of products.

In summary, the interaction of "soft" carbon nucleophiles with bis[(phenyl)iodonium] diyne salts has been employed to synthesize substituted bis-cyclopentene systems **3-5** in 66-77% isolated yields via dual, intramolecular, alkylidenecarbene 1,5-C–H bond insertions. The reaction of bis(iodonium) salts with NaTs affords a mixture of bis-cyclized, monocyclized and uncyclized disulfones, the ratio of which depends on both solvent polarity and temperature. Combined with the ease of handling and indefinite stability of the precursor iodonium salts **1a-c**, the mild reaction conditions and facile work-up provide a general procedure for the formation of a variety of bis-cyclopentenes of potential wide applicability in organic synthesis.

Acknowledgement. Financial support by the NCI of NIH (2RO1CA16903) is gratefully acknowledged.

References and Notes

1. Stang, P. J.; Tykwinski, R. R.; Zhdankin, V.V. *J. Org. Chem.* **1992**, *57*, 1861.
2. Formation of cyclopentenes from alkynyliodonium salts: Fischer, D. R.; Williamson, B. L.; Stang, P. J. *Synlett* **1992**, 535. Ochiai, M.; Kunishima, M.; Tani, S.; Nagao, Y. *J. Am. Chem. Soc.* **1991**, *113*, 3135. Kitamura, T.; Stang, P. J. *Tetrahedron Lett.* **1988**, *29*, 1887. Ochiai, M.; Kunishima, M.; Nagao, Y.; Fuji, K.; Shiro, M.; Fujita, E. *J. Am. Chem. Soc.* **1986**, *108*, 8281.
3. For iodonium salts in general see: Varvoglis, A. *The Organic Chemistry of Polycoordinated Iodine*; VCH Publishers: New York, 1992.
4. Review: Stang, P. J. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 274.
5. Stang, P. J. *In Methoden der Organischen Chemie (Houben-Weyl)*; Georg ThiemeVerlag: Stuttgart, 1989; Vol. E19b, Part I, pp. 84-165. Stang, P. J. *Chem. Rev.* **1978**, *78*, 383.
6. General procedure for the synthesis of bis-cyclopentene ring systems **3a-b**, **4a-b**, and **5a-b**. The respective iodonium triflate **1a-c** (1 eq) was added to a stirred THF solution of the enolate (2 eq, ~0.02M) of 2-phenyl- 1,3-indanedione or 2,2,5-trimethyl-1,3-dioxane-4,6-dione (generated via deprotonation by stirring with KO^{t}Bu in THF at room temperature for 30 min) and reacted at 25 °C for 30 min. The solvent was removed via rotary evaporation. The resulting oil was subjected to flash silica gel (200-400 mesh; 5 g, CH_2Cl_2) chromatography effecting removal of NaOTf. Addition of ether and hexanes to the CH_2Cl_2 solution until turbid followed by refrigeration overnight (–25 °C) affords **3a-b**, **4a-b** and **5a-b** as solids which were then filtered and could be further purified by recrystallization from CH_2Cl_2/hexanes.
7. General procedure for the reaction of iodonium salts **1a-c** with NaTs in benzene. The respective iodonium triflate **1a-c** (0.33 mmol) was added to a stirred suspension of NaTs (2.2 eq) in benzene (30 mL) at room temperature and allowed to react until the C≡C IR absorption of the iodonium salt was no longer observed, 2-5 h. The solvent was removed via rotary evaporator and the resulting oil was subjected to flash silica gel (200-400 mesh; 5 g, CH_2Cl_2) chromatography. Removal of iodobenzene by either chromatography (hexanes then CH_2Cl_2) or high vacuum affords product mixtures of **5**, **6**, and **7** suitable for NMR analysis. Bis-cyclized products **5a-c** were isolated by addition of hexanes and Et_2O to a CH_2Cl_2 solution of the product mixture and refrigeration (–25 °C) overnight.
8. General procedure for the reaction of iodonium salts **1a-c** with NaTs in CH_2Cl_2. The respective iodonium triflate **1a-c** (0.33 mmol) was added to a stirred suspension of NaTs (2.2 eq) in CH_2Cl_2 (30 mL) at either 25 °C or -43 °C and allowed to react for 1 h or 5 h respectively. Work-up was accomplished as described for the reaction in benzene.
9. General procedure for the reaction of iodonium salts **1a-c** with NaTs via aqueous exchange. A CH_2Cl_2 solution of the appropriate alkynyliodonium triflate salt **1a-c** (0.33 mmol, 30 mL) cooled to -78 °C was shaken with an aqueous solution of sodium *p*-toluenesulfinate (3 eq in 35 mL of H_2O, 25 °C) for approximately 3 min. The layers were separated and the aqueous phase was extracted once with CH_2Cl_2 (25 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and the volume reduced in vacuo. Work-up was accomplished as described for the reaction in benzene.
10. Gilbert, J. C.; Blackburn, B. K. *J. Org. Chem.* **1986**, *51*, 3656.

(Received in USA 8 *September* 1993*; revised* 18 *October* 1993; *accepted* 25 *October* 1993)