

Reaction of Alkynes with Iodine Monochloride Monochloride Revisited

Fabio Bellina,^{*,†} Francesca Colzi,[†] Luisa Mannina,^{‡,§}
Renzo Rossi,[†] and Stephane Viel[§]

Dipartimento di Chimica e Chimica Industriale, University of Pisa, via Risorgimento 35, I-56126 Pisa, Italy, Facoltà di Scienze M.F.N., University of Molise, via Mazzini 8, I-86170 Isernia, Italy, and Istituto di Metodologie Chimiche, CNR, Area della Ricerca di Roma/Montelibretti, via Salaria Km 29.300, I-00016 Monterotondo Stazione, Roma, Italy

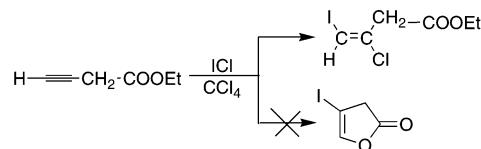
bellina@dcci.unipi.it

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Abstract: 6-*Exo-dig* and/or 7-*endo-dig* iodocyclization reactions of functionalized acetylenic derivatives with ICl are disfavored in comparison with the corresponding electrophilic addition reactions providing regioselectively (*E*)-1-chloro-2-iodoethene derivatives. On the contrary, 6-*endo-dig* and 5-*exo-dig* iodocyclizations of methyl ynoates with ICl seem to be favored in comparison with the corresponding electrophilic addition reactions.

In the past years, several investigations have been performed on the reaction of acetylenic compounds with iodine monochloride **1**^{1–13} and the synthetic applications of the resulting reaction products.^{7,10,12–14} As regards the reactions of **1** with alkylethyne,⁴ phenylethyne,⁴ internal acetylenic hydrocarbons,^{4,6} propiolic acid,² and ethyl 3-butynoate,³ it was found that the only reaction products isolated resulted from a regio- and stereoselective electrophilic addition. In particular, the reaction of terminal acetylenic hydrocarbons with **1** in acetonitrile was found to provide (*E*)-2-chloro-1-iodo-1-alkenes having 95–99% stereoisomeric purity,⁴ and similarly, ethyl (*E*)-2-chloro-1-iodo-3-butenate proved to be the only product of the reaction of **1** with ethyl 3-butynoate³ (Scheme 1). Interestingly, no five-membered iodolactonization product was

SCHEME 1. Reaction of Iodine Monochloride with Ethyl 3-Butynoate³



obtained in this last reaction even though a 5-*endo-dig* ring closure might occur according to Baldwin's rules¹⁵ (Scheme 1).

On the other hand, the reaction of **1** with propiolic acid gave (*E*)-1-chloro-2-iodopropenoic acid,² the regiochemistry different from that of the addition of **1** to ethyl 3-butynoate being explainable on the basis of the opposite polarity of the C–C triple bond of these acetylenic derivatives. More recently, it was shown that alkynylamine hydrochlorides react with **1** in refluxing THF to give regioisomeric mixtures of (*E*)-chloroiodoalkene derivatives in which the major products were those containing the chlorine atom attached to the olefinic carbon atom more distant from the nitrogen-containing group.⁸ It was also reported that treatment of α,β -acetylenic ketones with **1** in CH₂Cl₂, CH₂Cl₂/pyridine, or methanol provides mixtures of (*E*)- and (*Z*)-chloroiodoenones as major products in which the chlorine atom is linked to the olefinic carbon atom more distant from the carbonyl group.¹¹ On the contrary, it was found that treatment of **1** with acetylenic derivatives such as acetylenic β -diketones,⁷ 5-substituted (*Z*)-2-methyl-2-en-4-ynoic acids,^{10,16} stereodefined methyl 2-en-4-ynoates,⁹ methyl 2-(aryl-ethynyl)benzoates,⁹ and the corresponding carboxylic acids^{9,12} in CHCl₃ or CH₂Cl₂ solution provides products derived from electrophilic ring closure according to Baldwin's rules,¹⁵ i.e., 3-iodo-4*H*-pyran-4-ones, 6-substituted 5-iodo-3-methyl-2*H*-pyran-2-ones, 5-iodo-2*H*-pyran-2-ones, and 3-aryl-4-iodoisocoumarins, respectively, instead of compounds derived from an electrophilic addition reaction.

The variety of outcomes of the reactions involving the above-mentioned acetylenic compounds prompted us to investigate the reaction of a CH₂Cl₂ solution of **1** with ClCH₂CH₂Cl solutions either of the alkyl-substituted acetylenes **2a–d** or of the phenyl-substituted acetylenes **3a–g**, some of which might undergo electrophilic ring closure reactions, e.g., **2b**, **2c**, **3b**, and **3c**. This study included also propargyl alcohol **4**. In fact, no data were available in the literature on the regio- and stereochemical outcomes of the reaction of **1** with all these compounds in CH₂Cl₂ and ClCH₂CH₂Cl solution. We thought it right to perform the investigation on the stereochemistry of the reactions leading to addition products by NMR spectroscopy using NOESY experiments. In fact, the stereochemistry of the products derived from an electrophilic addition of **1** to alkynes has been established

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(16) The reaction between **1** and 5-substituted (*Z*)-2-methyl-2-en-4-ynoic acids provides a mixture of 6-substituted 5-iodo-3-methyl-2*H*-pyran-2-ones and (*E*)-3-methyl-5-ylidene-5*H*-furan-2-ones in which these last compounds are the minor components (see: ref 10).

[†] University of Pisa.

[‡] University of Molise.

[§] Istituto di Chimica Nucleare, CNR.

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(2) Andersson, K. *Chem. Scr.* **1972**, *2*, 117.

(3) Tendil, J.; Verney, M.; Vessiere, R. *Tetrahedron* **1974**, *30*, 579.

(4) Uemura, S.; Okazaki, H.; Onoe, A.; Okano, M. *J. Chem. Soc., Perkin Trans. 1* **1977**, 676.

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(9) Biagetti, M.; Bellina, F.; Carpita, A.; Stabile, P.; Rossi, R. *Tetrahedron* **2002**, *58*, 5023.

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(13) Yao, T.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 5936.

(14) Luo, F. T.; Lai, J. H.; Shae, J. C. *Bull. Inst. Chem., Acad. Sin.* **1987**, *34*, 17.

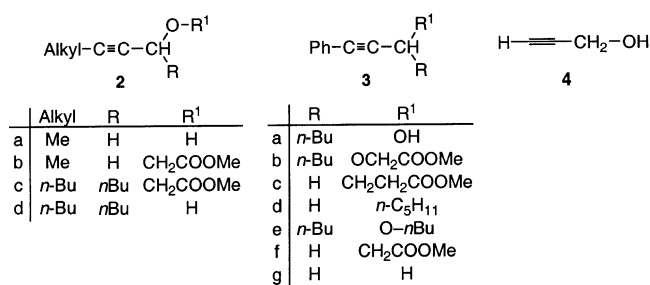
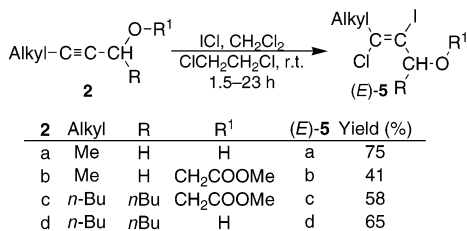


FIGURE 1. Chemical structures of alkynes **2a–d**, **3a–g**, and **4**.

SCHEME 2. Reaction between Alkynes 2a–d and Iodine Monochloride



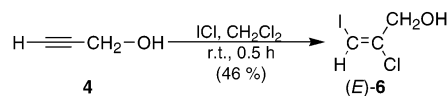
so far on the basis of a comparison between the ¹³C chemical shifts calculated from substituent parameters for vinyl derivatives¹⁷ and the corresponding ¹³C chemical shifts observed⁴ or taking into account the relative stability of the stereoisomeric addition products obtained in this addition reaction.¹¹

Our studies began with the reaction of ClCH₂CH₂Cl solutions of alkynes **2a–d** with 1 equiv of **1** in CH₂Cl₂ solution at room temperature, and we found that the addition proceeded until completion in 1.5–23 h to give the corresponding chloriodoalkenes **5a–d** in 41–75% isolated yields (Scheme 2).¹⁸ Stereoisomerically pure compounds (*E*)-**5b–d** were found to be the only reaction products, but (*E*)-**5a** had ca. 90% stereoisomeric purity (Scheme 2).^{18,19}

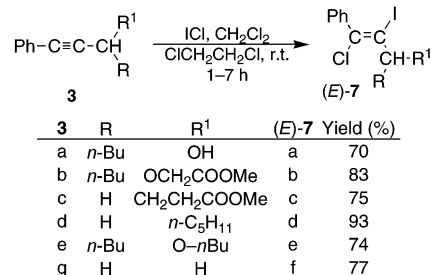
The regiochemical outcome of these addition reactions was established taking into account the different effects exerted by chlorine and iodine atoms on the chemical shift of the carbon to which they were directly bonded. In fact, a chlorine atom induces a downfield shift of the carbon resonance due to its high electronegativity, whereas an iodine atom leads to an upfield shift of the carbon resonance due to the “heavy atom effect”.²⁰

This regiochemical outcome corresponded to that predicted by the Markovnikov rule.^{8,21} On the other hand, the *E*-configuration of compounds **5a–d** was established by NOESY experiments that showed the absence of cross-

SCHEME 3. Reaction between Iodine Monochloride and Propargyl Alcohol



SCHEME 4. Reaction between Iodine Monochloride and Phenyl-Substituted Alkynes 3



peaks between the protons of the CH₃ or CH₂ groups adjacent to the C–Cl bond and the protons of the CH₂ or CH groups adjacent to the C–I bond.²²

Similarly, a NOESY experiment allowed us to establish the *E*-configuration of **6**, which was obtained stereoisomerically pure in 46% yield by reaction of **4** with **1** (Scheme 3).²³

We next investigated the reaction of **1** with alkynes **3a–e,g** and found that the reaction was completed in 1–7 h at room temperature. Stereoisomerically pure compounds (*E*)-**7a–f**, which were obtained in 70–93% isolated yields, were found to be the only reaction products (Scheme 4).¹⁸

The regiochemical outcome of these reactions was established in a way similar to that used for the addition reactions involving **2a–d**. On the other hand, for the configurational assignment to compounds **7**, initially we used NOESY experiments and, unlike what was observed for compound **5**, we noticed the presence of cross-peaks between the aromatic protons in the *o*- and *o'*-positions of the phenyl group of these compounds and the protons of the CH₂ or CH groups in the α -position to the C–C double bond of these substances. However, these cross-peaks had weak intensity and their presence could be justified by the *E*-configuration of compounds **7**.

In fact, molecular models²⁴ showed that the distance between the allylic protons of these compounds and the aromatic protons in the *o*- and *o'*-positions of their phenyl group was about 5 Å, i.e., in agreement with that expected on the basis of the intensity of the observed cross-peaks.²⁵

This configurational assignment was confirmed by determination of the dipolar moment of compounds (*E*)-

(17) Stothers, J. B. *Carbon-13 NMR Spectroscopy*; Academic Press: New York, 1972; pp 71 and 184.

(18) All new compounds were characterized by elemental analysis, EI-MS spectrometry, and IR, ¹H and ¹³C NMR spectroscopy. The structures of compounds (*E*)-**5a–d**, (*E*)-**6**, and (*Z*)-**7a–e** were assigned on the basis of their ¹H and ¹³C NMR spectra and by a combination of two-dimensional NMR techniques, which included ¹H–¹H COSY, ¹H–¹³C COSY, ¹H–¹³C HSQC (heteronuclear single quantum coherence) and ¹H–¹³C HMBC (heteronuclear multiple-bond correlation).

(19) GLC analysis showed that (*E*)-**5a** was contaminated by less than 10% of (*Z*)-**5a**.

(20) Friebolin, H. *Basic One- and Two-Dimensional NMR Spectroscopy*; VCH Publisher: New York, 1991; p 56.

(21) Reference 1, p 278.

(22) This assignment supports the formation of a cyclic iodonium intermediate similar to that previously proposed for the electrophilic addition of I–X species to dialkyl acetylenes [Bassi, P.; Tonellato, U. *J. Chem. Soc., Perkin Trans. 2* **1973**, 669].

(23) The regiochemistry of **6**, which was assigned on the basis of a principle similar to that used to establish the structures of **5a–d**, proved to be in agreement with that of the products of the reaction of **1** either with alkylethyne in acetonitrile (see ref 4) or with ethyl 3-butynoate in CCl₄, AcOEt, AcOH, or EtCOOH solution (see ref 3).

(24) We used MOPAC 97 software for Chem3D v. 5 (MNDO method) by Cambridgesoft.

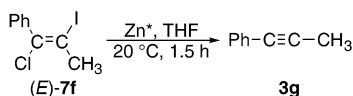
(25) Claridge, T. D. W. *High-Resolution NMR Techniques in Organic Chemistry*; Pergamon-Elsevier Science Ltd.: Oxford, 1999; p 303.

TABLE 1. Comparison between the Measured Values $\mu_{(\text{gas})\text{exp}}$ of the Dipolar Moment of Compounds **7d and **7f** and the Theoretic Values $\mu_{(\text{gas})\text{theor}}$ of the Dipolar Moments of These Compounds Having *E*- and *Z*-Configuration**

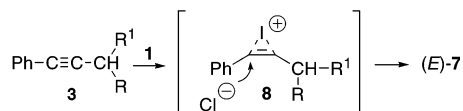
compound	$\mu_{(\text{gas})\text{exp}}$	dipolar moment (in Debye)	
		$\mu_{(\text{gas})\text{theor}}$	
		(<i>E</i>)- 7	(<i>Z</i>)- 7
7d	0.74 ^a	0.97	2.68
7f	0.96 ^b	1.08	2.63

^a The corresponding value of $\mu_{(\text{sol})\text{exp}}$ was 0.67. ^b The corresponding value of $\mu_{(\text{sol})\text{exp}}$ was 0.87.

SCHEME 5. Reaction between **7f and Activated Zinc Metal**



SCHEME 6. Postulated Intermediates of the Reaction between **1 and Alkynes **3****



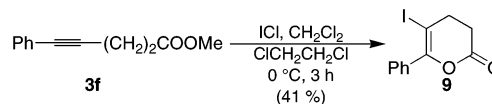
7d and (*E*)-**7f**.^{26,27} In fact, as shown in Table 1, the measured values of $\mu_{(\text{gas})\text{exp}}$ for **7d** and **7f**, which were higher than about 10% of the corresponding values obtained at infinite dilution, were found to be similar to the theoretic values of $\mu_{(\text{gas})\text{theor}}$ ²⁴ for the same *E*-configured substances in the form of a gas and very different from the theoretic values for (*Z*)-**7d** and (*Z*)-**7f** in the form of a gas.

A further confirmation of the *E*-configuration of compounds **7** was obtained from the results of the reaction of **7f** with activated zinc metal²⁸ in THF at room temperature. As expected, this reaction did not provide the organometallic reagent derived from insertion of zinc into the C–I bond of **7f**, but gave via an *anti*-elimination process alkyne **3g** as the only reaction product (Scheme 5).²⁹

Thus, the regio- and stereochemical results of the reaction of **1** with compounds **3** could be rationalized assuming that this electrophilic addition reaction involves an *anti*-attack of the chloride anion onto the iodonium ion **8** (Scheme 6).

Finally, we completed our investigations by examining the reaction of **1** with the phenyl-substituted acetylene **3f**, and we found that, when this reaction was carried out under experimental conditions similar to those employed for the preparation of (*Z*)-**7a–e**, no addition product was obtained. In fact, this reaction provided only compound **9**, which was derived from an electrophilic iodolactonization reaction (Scheme 7).

SCHEME 7. Iodolactonization of **3f**



A first conclusion that can be drawn from the above-reported results is that 6-*exo-dig* and/or 7-*endo-dig* electrophilic ring closures do not occur when functionalized acetylenes, containing a nucleophilic site at the δ position from their C–C triple bond (e.g., compounds **2b**, **2c**, **3b**, and **3c**), are reacted with **1** in CH_2Cl_2 and/or $\text{ClCH}_2\text{CH}_2\text{Cl}$ solution. In fact, these ring closures proved to be disfavored in comparison with the corresponding electrophilic addition reaction. On the contrary, as shown either from the result illustrated in Scheme 7 or from those concerning the reaction between **1** and 5-substituted (*Z*)-2-methyl-2-en-4-ynoic acids,¹⁰ stereodefined methyl 2-en-4-ynoates,⁹ and methyl 2-(arylethynyl)benzoates⁹ or the corresponding carboxylic acids,^{9,12} 6-*endo-dig* and 5-*exo-dig* ring closures seem to be favored in comparison with the electrophilic addition reaction.

This study also allowed us to establish that the electrophilic addition of **1** to alkyl- and phenyl-substituted acetylenes in CH_2Cl_2 and $\text{ClCH}_2\text{CH}_2\text{Cl}$ solution provides regio- and stereoselectively (*E*)-chloroiodoalkenes containing the iodine atom linked to the olefinic carbon atom more distant from the alkyl or the phenyl group.

Finally, it is worth mentioning that, whereas the values of the ¹³C chemical shifts of the acetylenic carbon atoms of alkynes **2** and propargyl alcohol **4** could allow us to predict correctly that the iodine and chlorine moieties of **1** will add to the more shielded and deshielded acetylenic carbon atoms of these compounds, respectively,^{30,31} the values of the ¹³C chemical shifts of the acetylenic carbon atoms of alkynes **3** could not be used for predicting the regioisomeric outcome of the electrophilic addition of **1** to these alkynes.

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Supporting Information Available: Experimental procedures, characterization data for **2a–d**, **3a–f**, (*E*)-**5a–d**, (*E*)-**6**, (*Z*)-**7a–f**, and **9**, and lists of the ¹³C chemical shifts of the acetylenic carbon atoms of alkynes **2** and **3** and of the olefinic carbon atoms of (*E*)-**5a–d** and (*Z*)-**7a–e** (Tables 1–3). This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO035372F

(26) Shoemaker, G. *Experiments in Physical Chemistry*; McGraw-Hill: New York, 1967; Chapter XII.

(27) Debou, A.; Masson, S.; Thuiller, A. *Bull. Soc. Chim. Fr.* **1975**, 11–12, 2493.

(28) Knochel, P.; Rao, C. J. *Tetrahedron* **1993**, 49, 29.

(29) An elimination process leading to alkynes has also been recently observed when (*E*)-1,2-dibromoethene derivatives were reacted with THF solutions of arylmagnesium bromides lacking ortho substituents in the presence of a catalytic amount of $\text{PdCl}_2(\text{PPh}_3)_2$ [Rathore, R.; Deselnicu, M. I.; Burns, C. L. *J. Am. Chem. Soc.* **2002**, 124, 14832].

(30) The chemical shifts of acetylenic carbon atoms have already been used as an approximative measure of the zonal charge density [Meier, H.; Stavidrou, E.; Storek, C. *Angew. Chem., Int. Ed. Engl.* **1986**, 25, 809; Rosenberg, D.; Drenth, W. *Tetrahedron* **1971**, 27, 3893].

(31) Two tables containing either the chemical shift values of the acetylenic carbon atoms of compounds **2**, **3**, and **4** or the resulting chemical shift differences $\Delta\delta$ are reported in the Supporting Information.