ORGANIC LETTERS

2008
Vol. 10, No. 6
1219−1221

Stereoselective Synthesis of Trisubstituted *E*-Iodoalkenes by Indium-Catalyzed *syn*-Addition of 1,3-Dicarbonyl Compounds to 1-Iodoalkynes

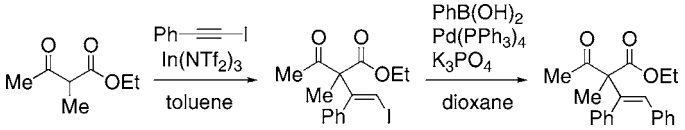
Hayato Tsuji, Taisuke Fujimoto, Kohei Endo,[†] Masaharu Nakamura,[‡] and Eiichi Nakamura*

Department of Chemistry, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

nakamura@chem.s.u-tokyo.ac.jp

Received January 16, 2008

ABSTRACT



Indium-catalyzed addition of 1,3-dicarbonyl compounds to 1-iodo-1-alkynes takes place exclusively in a *syn*-fashion to produce *E*-iodoalkenes. The iodine atom serves both as an activating group and as a group that controls the regioselectivity of the addition. The *E*-alkenyl iodide product can be further derivatized using either a one-pot or a two-pot procedure into trisubstituted olefins in high overall yield with retention of the stereochemistry.

Addition of a metal enolate to an unactivated olefin[1] and an unactivated acetylene[2,3] is an emerging class of reactions in metal enolate chemistry. We previously developed an indium-catalyzed addition reaction for a variety of 1,3-dicarbonyl compounds to alkynes[2] that results in alkenylation of the carbonyl compounds at the 2-position. The reaction, however, tolerates the use of only 1-alkynes (and 1-silyl-1-alkyne) but not internal alkynes, and hence the reaction is useful only for the synthesis of 1,1-disubstituted alkenes. During our attempt to expand the scope of the reaction, we found that an iodine atom assists the addition reaction, and thus the reaction with 1-iodoalkyne produces, in high yield and with 100% regio- and stereoselectivity, the expected substituted iodoalkenes (eq 1), from which the synthesis of trisubstituted olefins[4−8] has been achieved readily through conversion of the iodine atom to an organic group.

[†] Present address: Department of Chemistry and Biochemistry School of Advanced Science and Engineering, Waseda University, Ohkubo, Shinjuku-ku, Tokyo 169−8555, Japan.

[‡] Present address: International Research Center for Elements Science Institute for Chemical Research, Kyoto University, Uji, Kyoto 611−0011, Japan.

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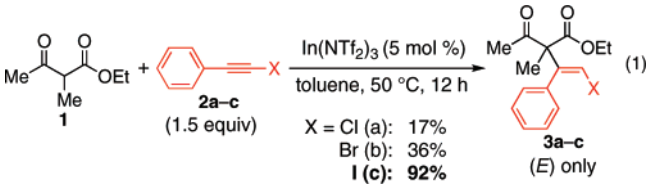
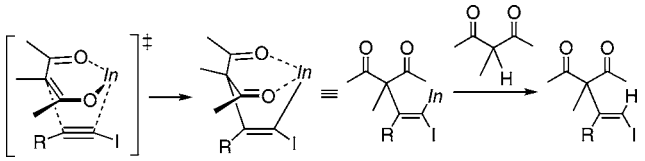
10.1021/ol800105r CCC: $40.75
Published on Web 02/27/2008



The use of 1-haloalkyne as an acceptor for the addition of a metal enolate was a priori not a rational synthetic strategy for several reasons. For instance, the use of a halogen atom for activation of a π-conjugated system is unprecedented, and the possible intermediate of the reaction would be an indium carbenoid (Scheme 1) that may be too unstable

Scheme 1. Proposed *syn*-Addition and Formation of an *E*-Product



to exist. Nonetheless, we tried the reaction for 1-chloro-, 1-bromo-, and 1-iodo-2-phenylacetylenes. Thus, ethyl 2-methylacetoacetate (**1**) and 1.5 equiv of (haloethynyl)benzene (**2a**−**c**) were allowed to react in the presence of 5 mol % of $In(NTf_2)_3$ in toluene at 50 °C for 12 h, and we obtained the expected haloalkenes **3a**−**c** as a single isomer in all cases. The yield increased in the order of the chloro, bromo, and iodo group, and the iodoacetylene gave the desired product in the best yield of 92%. It was essential to use a powerful catalyst $In(NTf_2)_3$ instead of $In(OTf)_3$ to obtain a synthetically significant yield.[2c,e] The reaction was entirely regioselective and *E*-stereoselective. When we used ethyl acetoacetate in place of **1**, we obtained an intractable product mixture. On the basis of the mechanistic hypothesis illustrated in Scheme 1, we consider that the observed regioselectivity indicates that the intermediate of the reaction is an indium carbenoid species.

The structure of the product was unambiguously determined by X-ray crystallographic analysis of the product obtained from ethyl 2-oxocyclopentanecarboxylate and 1-iodo-2-phenylacetylene (which appears in Table 1, entry 8) as

Table 1. Examples of 1,3-Dicarbonyl Compounds Used in Eq 2

	substrate				
entry	R^1	R^2	R^3	time (h)	yield (%)
1	Me	Me	OEt	4	92
2	Me	Me	OAllyl	4	89
3	Ph	Me	OEt	60	93
4	*t*-Bu	Me	OMe	24	0
5	Me	Ph	OEt	24	0
6	Me	F	OEt	16	93
7	EtO	Me	OEt	48	81
8	$-(CH_2)_3-$		OEt	6	90
9	$-(CH_2)_3-$		OBn	6	94
10	$-(CH_2)_3-$		Me	24	89

shown in Figure 1: the configuration of the compound is *E*. We assume that other reactions shown in Table 1 took place in the same manner.

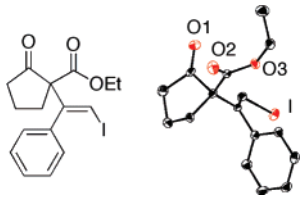
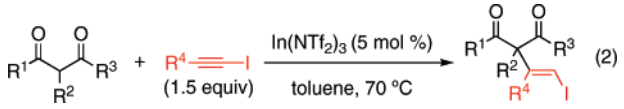


Figure 1. ORTEP drawing (50% probability for thermal ellipsoid). Hydrogen atoms are omitted for clarity.

The *E* configuration and the regioselectivity of the product is consistent with the cyclic transition state shown in Scheme 1, which is based on the one proposed previously for 1-alkyne on the basis of calculations.[2d] In this transition state, the indium and the iodine atoms are attached to the same atom, and the latter is considered to exert special stabilization effects. The difference among **2a**, **2b**, and **2c** suggests that the iodine atom has a particularly favorable effect on the addition reaction.

A variety of 1,3-dicarbonyl compounds reacted smoothly with (iodoethynyl)benzene (**2c**) at 70 °C, and the results are summarized in Table 1 (eq 2, R^4 = Ph).[9] All of the addition reactions in this study afforded a single stereo- and regioisomer.



The reaction of 2-methyl-3-oxobutanoic acid ethyl and allyl esters was complete in 4 h and afforded the desired

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product in 92 and 89% yield, respectively (entries 1 and 2). When the R^1 group was a phenyl group, the reaction slowed down but still afforded the product in good yield (93%, entry 3). However, the reaction did not take place at all when R^1 was a *tert*-butyl group (entry 4). The R^2 group at the 2-position also exerts a large effect. When R^2 was a phenyl group, the reaction did not take place at all (entry 5). We consider that the phenyl group inhibited the reaction by its steric bulk. A 2-fluoroester was less reactive than **1**, but still afforded the product in 93% yield (entry 6). A cyclic ketoester also took part in the reaction and afforded the expected adduct in 90% yield (entry 8). Diethyl methylmalonate and a cyclic diketone were found to be quite reactive toward the iodoacetylene and gave the expected products in high yields (entries 7 and 10). They were less reactive than the corresponding ketoester counterparts (entry 1, 92% after 4 h, vs entry 7, 81% after 48 h; entry 8, 90% after 6 h, vs entry 10, 89% after 24 h).

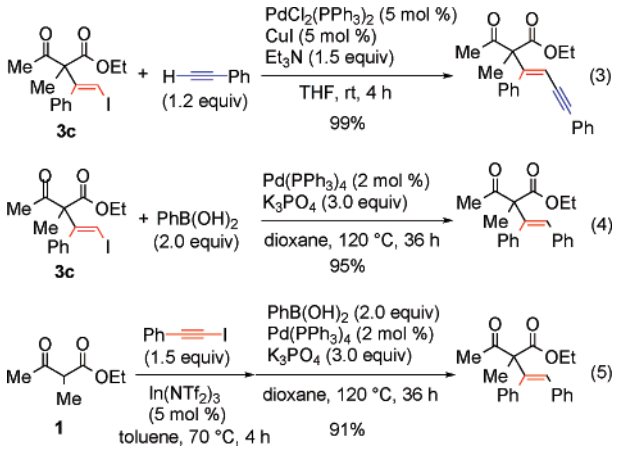
We next examined the scope of the iodoalkynes using *β*-ketoester **1** (Table 2). Electron-rich iodoalkynes are somewhat thermally labile but quite reactive under the present reaction conditions. Thus, the reaction of the ketoester **1** with *p*-(iodoethynyl)anisole was complete in 1.5 h at 70 °C and afforded the product in 89% yield (entry 1). In contrast, electron-deficient alkynes are thermally stable but less reactive. The reaction at higher temperature and for a longer time, however, afforded the product in excellent yield (entries 2 and 3). This reactivity profile agrees more closely with the lower reactivity of **2a** and **2b** than with **2c** (eq 1), suggesting that the reaction is an electrophilic addition reaction. Interestingly, the reaction of the naphthalene-substituted iodoacetylene afforded the product in high yield as a 1:1.5 diastereomeric mixture (entry 4). The diastereoisomerism is due to the central chirality at the 2-position of the 1,3-dicarbonyl group and the axial chirality between the naphthyl and the iodovinyl moieties. An aliphatic alkyne afforded the desired product in moderate yield (48%, entry 5).

Table 2. Examples of Iodoalkynes $R^4-C\equiv C-I$[a]

entry	R^4	conditions	yield (%)
1	MeO–C$_6$H$_4$–	70 °C, 1.5 h	89
2	MeO$_2$C–C$_6$H$_4$–	100 °C, 72 h	93
3	Br–C$_6$H$_4$–	100 °C, 60 h	88
4	2-naphthyl	70 °C, 12 h	95[b]
5	C_6H_{13}–	70 °C, 12 h	48

[a] All reactions were carried out using the same reaction conditions shown in eq 2 except for the reaction temperatures for some reactions. [b] Ca. 1:1.5 mixture of diastereomer was obtained.

Finally, we describe the transformation of the addition product into trisubstituted olefins. As illustrated in eq 3, the alkenyl iodide **3c** was quantitatively and stereospecifically coupled with phenylacetylene under the Sonogashira conditions to give the conjugated enyne. Similarly, the Suzuki coupling with phenylboronic acid stereospecifically afforded the diphenyl-substituted alkenes in excellent yield (eq 4). Equation 5 illustrates a one-pot coupling of 1,3-dicarbonyl compound **1**, iodoacetylene, and phenylboronic acid, which took place in 91% overall yield. Thus, the seemingly problematic presence of the indium catalyst in the second palladium-catalyzed step did not pose any serious problems.



In conclusion, we have found that 1-iodo-1-alkynes serve as useful acceptors in the catalytic addition of the indium enolate of 1,3-dicarbonyl compounds. The role of the iodine atom in this reaction is intriguing in several respects. The observed regioselectivity implies the involvement of a rather stable transient indium carbenoid and also suggests that this stability is responsible for the regioselectivity observed in this reaction. The reaction can be viewed as an electrophilic addition of an indium enolate to the acetylene[2d] rather than a nucleophilic addition that is the standard reactivity of metal enolates, and it is in this context that the iodine group activates the alkyne and controls the regioselectivity. The expected synthetic utilities of the products are no less interesting than the mechanism and will be the subject of further studies.

Acknowledgment. This research was supported by KAKENHI provided by MEXT/JSPS (to E.N., Grant No. 18105004) and the Global COE Program for Chemistry Innovation (to H.T. and T.F.).

Supporting Information Available: Experimental details and CIF file of the compound shown in Figure 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) *Caution:* Haloalkynes are unstable under light, particularly at high temperature and therefore the reaction vessel must be protected from ambient light. **A Typical Procedure**: (*E*)-Ethyl 2-ethanoyl-4-iodo-2-methyl-3-phenylbut-3-enoate (**3c**). A mixture of ethyl 2-methylacetoacetate (288 mg, 2.00 mmol), (iodoethynyl)benzene (684 mg, 3.00 mmol), and $In(NTf_2)_3$ (95.5 mg, 0.100 mmol) in toluene (2.0 mL) was heated in the dark at 70 °C for 4 h. The mixture was filtered through a pad of silica gel and concentrated. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate = 95/5) to obtain the title compound as a yellow oil (655 mg, 88%). The yields on 100 mg runs averaged close to 92%.