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Iodo Meyer–Schuster Rearrangement of 3-Alkoxy-2-yn-1-ols for β-Mono (Exclusively Z-Selective)-/Disubstituted α-Iodo-α,β-Unsaturated Esters

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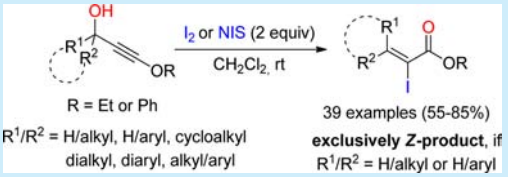
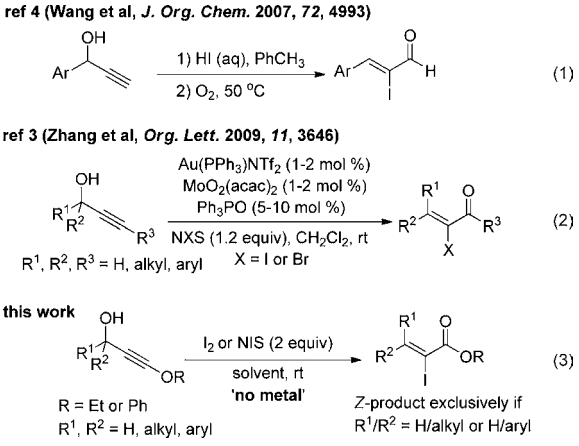
Supporting Information

ABSTRACT: We herein present the iodo Meyer–Schuster rearrangement of 3-alkoxypropargyl alcohols for α-iodo-α,β-unsaturated esters using iodine or NIS in dichloromethane at ambient temperature. Substrates prepared from both aldehydes and ketones are found to be equally good feedstock for the reaction to produce β-mono- and -disubstituted products. Irrespective of the substitution, substrates prepared from aldehydes gave *Z*-isomers exclusively.



Meyer–Schuster rearrangement offers an efficient approach for the construction of a variety of highly substituted (di-, tri-, and tetra-) conjugated carbonyl compounds and α,β-unsaturated esters.[1,2] Given the catalytic nature of the reaction, this has become a versatile alternative to the classical aldol condensation and Wittig reaction while largely expanding the use of readily available propargyl alcohols. A number of metal systems along with several Bronsted acids have been identified for the successful execution of these transformations. In the same line, Zhang et al. reported (Scheme 1, eq 2) an iodo Meyer–Schuster rearrangement[3] through a novel concept for the general synthesis of α-iodo-α,β-unsaturated carbonyl compounds where an Au catalyst was needed for the alkyne activation followed by Au–I exchange, a Mo catalyst for the hydroxyl migration, and a phosphine catalyst to suppress the byproducts. Prior to that, a similar transformation (with a restriction to aryl and terminal propargyl alcohols) was reported by Wang and Chen[4] for the α-iodo-α,β-unsaturated aldehydes, by using iodide (aqueous HI in toluene) rather than an iodonium ion through a different pathway of involving iodoallene intermediates and their oxygen-mediated oxidation. The Meyer–Schuster rearrangement is yet to be extended to the alkoxy propargyl alcohols for the synthesis of α-iodo-conjugated esters which are valuable subunits for the stereodefined entry to highly substituted olefins through modification of the ester functional group and by the metal catalyzed coupling reactions on the vinyl iodide unit. Filling this gap, and as part of our ongoing program of unveiling the new reactions of functionalized alkynes through electrophilic activation,[5] we herein report the synthesis of α-iodo-α,β-unsaturated esters with both β-mono- and -disubstitution. This was achieved using only I_2 or NIS as reagents with the exclusion of any assistance of metal catalysts, and under very mild conditions.

Scheme 1. Synthesis of α-Halo Conjugated Carbonyls



Although the synthesis of α-halo-conjugated esters through a halogenated Wittig reaction and some other approaches are reported in the literature,[6] the protocols were mostly restricted to aldehydes as substrates or for the bromoadducts. And the outcome of the reactions often seriously suffered from the formation of mixture of diastereomers, leaving its general synthesis still a formidable challenge to synthetic chemists. The method we present here is not only equally applicable for the substrates from both aldehydes and ketones but also highly stereoselective (*Z*-only) for the β-monosubstituted adducts.

Initially we selected a known substrate **1a**[7] for optimization studies. With the experience of activating the ethoxy alkynes using I_2 without the assistance of any metal catalyst,[5e] we treated **1a** with I_2 in CH_2Cl_2 (Table 1, entry 1). Unfortunately, it

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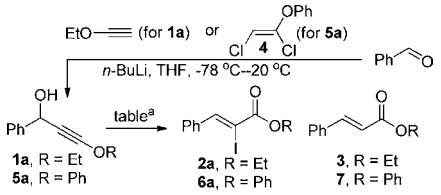
Table 1. Optimization of Reaction Conditions



entry	substrate	reagent	base	solvent	temp/time (h)	product (ratio)[c]	yield[b]
1	**1a**	I_2	–	CH_2Cl_2	rt/0.5	**2a** + **3** (3:2)	68%
2	**1a**	I_2	–	CH_2Cl_2	0 °C/1.5	**2a** + **3** (6:1)	62%
3	**1a**	I_2	–	DCE	rt/0.5	**2a** + **3** (2.3:1)	65%
4	**1a**	I_2	–	THF	rt/0.5	**2a** + **3** (7:1)	58%
5	**1a**	I_2	–	toluene	rt/0.5	**2a** + **3** (2:1)	55%
6	**1a**	I_2	$NaHCO_3$	CH_2Cl_2	rt/0.5	**2a** + **3** (3:1)	60%
7	**1a**	I_2	Na_2CO_3	CH_2Cl_2	rt/0.5	**2a** + **3** (3:1)	60%
8	**1a**	I_2	K_2CO_3	CH_2Cl_2	rt/0.5	**2a** (*E*/*Z*)	59%
9	**1a**	NIS	–	CH_2Cl_2	rt/1	**2a** (*E*/*Z*)	65%
10	**1a**	NIS	–	DCE	rt/1	**2a** (*E*/*Z*)	63%
11	**1a**	I_2	TEA	CH_2Cl_2	rt/12	–	–
12	**1a**	I_2	Py	CH_2Cl_2	rt/12	–	–
13	**1a**	**I_2**	**K_2CO_3**	**toluene**	**rt/5**	**2a**	**65%**
14	**5a**	**I_2**	–	**CH_2Cl_2**	**rt/5**	**6a**	**75%**
15	**5a**	**NIS**	–	**CH_2Cl_2**	**rt/10**	**6a**	**70%**

[a]2 mmol of reagent were added to 1 mmol of substrate in solvent (0.25 M). [b]Isolated yield. [c]Ratio of the products was calculated from ^{1}H NMR.

produced an inseparable mixture of required product **2a** and non-iodo Meyer−Schuster product **3**. The fate of the reaction did not change with the variation in temperature (0 °C, entry 2) and solvent (DCE, THF or toluene, entries 3−5) or by the addition of the base $NaHCO_3$ or Na_2CO_3 (entries 6−7).

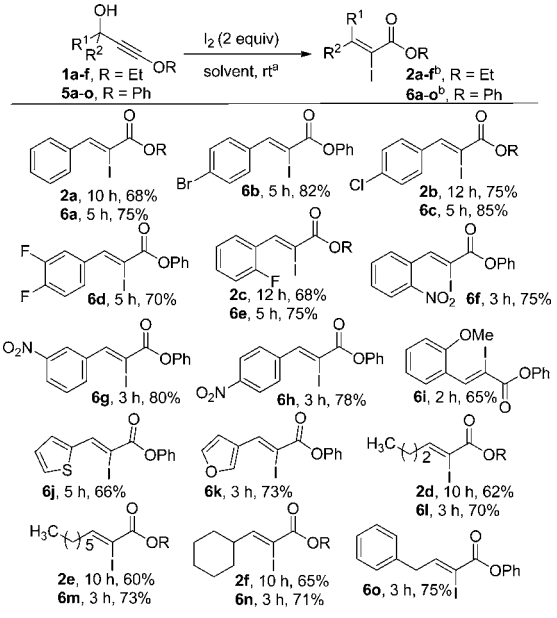
We reasoned that the high reactivity of ethoxyalkyne makes it sensitive to the acidic nature of the reaction medium and as a result led to proton assisted Meyer−Shuster rearrangement. Use of K_2CO_3 with I_2 (entry 8) or NIS in place of I_2 (entries 9 and 10) suppressed the formation of byproduct **3**, but the required product **2a** was formed as an inseparable mixture of *E*/*Z* isomers. Strangely, organic bases TEA and Py (entries 11 and 12) produced an unidentified intermediate which slowly converted to the product during the purification, making the approach unreliable. Finally, to our pleasure, use of K_2CO_3 as a base with I_2 in nonpolar solvent, toluene, cleanly afforded **2a** as a single isolable product in 65% yield.

Meanwhile, we worked with phenoxy propargyl alcohol **5a** (prepared by the addition of phenoxy acetylide[8] to benzaldehyde) instead of **1a** for the following reasons: (1) the reactivity of phenoxyalkyne is relatively less due to the sharing of oxygen's lone pair electrons between the alkyne and phenyl ring, and hence it may not undergo undesired Meyer−Schuster rearrangement; (2) the shelf life of **5** is very high compared to **2** which slowly forms **3** on standing; (3) although commercially available, ethoxyacetylene is expensive whereas phenoxy dichloroethene **4** (equivalent of phenoxy acetylene) can be synthesized in large scale (more than 100 g) from cheaply available trichloroethene and phenol.

Realizing our conception, the reaction of **5a** with I_2 occurred very selectively at rt to afford the required product **6a** as a sole outcome in 75% yield while no undesired Meyer−Shuster product (**7**) was detected (entry 14). Delightedly, **6a** was found to be formed exclusively as a *Z*-isomer (*vide infra*, Scheme 5). NIS in CH_2Cl_2 also worked well for the transformation but with a prolonged reaction time (entry 15, 70% **6a**).

With optimal reaction conditions (I_2, CH_2Cl_2, rt) in hand, the scope and limitations of this reaction were then investigated. As is evident from Scheme 2, the iodo Meyer−Shuster rearrangement was found to be quite effective over a wide range of phenoxy alcohols. Similar to **5a**, halo (Br, Cl, F) substituted substrates **5b−e** afforded, upon exposure to I_2 in CH_2Cl_2, the corresponding products **6b−e** in 70−85% yields. Substrates

Scheme 2. Iodo Meyer Schuster Rearrangement of Substrates 1 and 5 Prepared from Aldehydes



[a]1 mmol of **1** or **5** in 4 mL of solvent (toluene for **1** and CH_2Cl_2 for **5**) was added to 2 mmol of I_2 (and 2 equiv of K_2CO_3 in the case of **1**) at rt, and the contents were stirred until completion (TLC). [b] Isolated yields.

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5f–h with an electron-withdrawing nitro group also gave an excellent outcome (**6f–h** in 75–80% yields) while their electron-rich counterpart **5i** resulted in moderate yield (65%) of the product **6i**. Pleasingly, heteroaryl substituted adducts **6j** and **6k** were also obtained in good yields (66–73%) under the standard conditions.

Remarkably, the reaction on alkyl substituted substrates **5l–n** also suffered neither selectivity issues producing exclusively Z-isomers nor low conversion rates which was expected due to relatively tough C–OH bond cleavage compared to that of benzyl alcohol counterparts **5a–k**. Thus, the products **6l–n** were obtained in 70–73% yields. The result indicated that the total *Z*-selectivity is only because of steric hindrance and not due to conjugation factors. Notably, skipped olefinic product **6o** was also smoothly obtained in 75% yield. Additionally, ethyl counterparts (**2a–f**) of a few of the products were synthesized from corresponding ethoxypropargyl alcohols (**1a–f**), in their standardized conditions (I_2, K_2CO_3, toluene, rt) to expand the scope of the approach. The yields of the phenoxy conjugated esters (**6a–o**, 65–85%) were higher than those of ethyl conjugated esters (**2a–f**, 60–75%)

Moving forward, we chose substrates prepared from ketones which would give *β*-disubstituted adducts. Initially, when we subjected the substrates **8a–c** (Scheme 3), synthesized from aliphatic ketones, to I_2 in CH_2Cl_2 (rt or 0 °C), the eliminated products **9a–c** (respectively) were formed instantly and exclusively. While assisted by an acidic atmosphere created by I_2, the presence of an adjacent aliphatic proton to tertiary alcohol tempted the substrate to take an alternative pathway of elimination before allowing the expected iodo Meyer–Schuster rearrangement. Use of a base also did not change the course of the reaction.

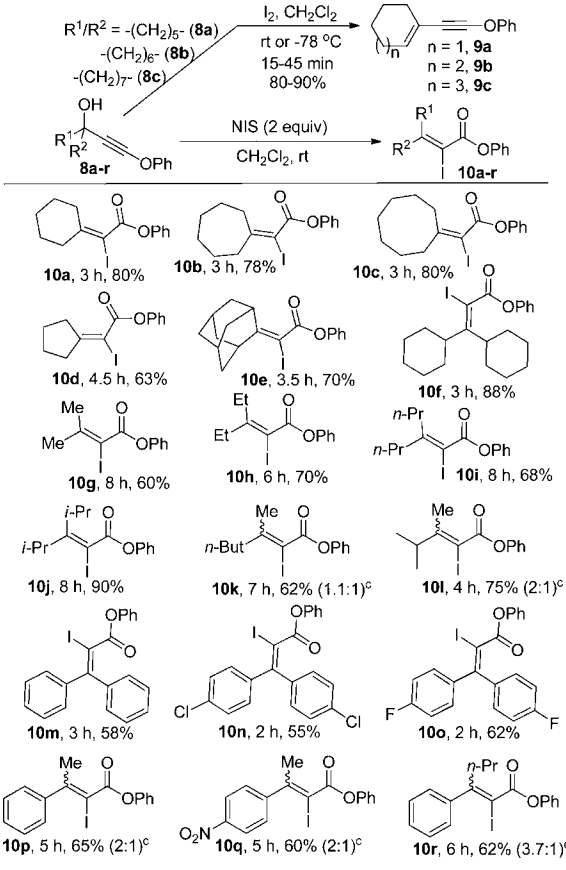
We then switched to the alternative nonacidic reagent, NIS (which was proved to be almost equally effective as is evident from Table 1), for the transformation. Pleasingly, the expected transformation of **8a** to **10a** occurred very smoothly (80%) with 2 equiv of NIS in CH_2Cl_2 at rt.

Similarly, substrates **8b–d**, prepared from other cyclic ketones, also underwent the title transformation to afford the corresponding products (**8b–d**) in excellent yields (63–80%). The sterically hindered substrates **8e** and **8f**, prepared from adamantanone and dicyclohexyl ketone respectively, also smoothly reacted under the optimized conditions to give the corresponding products (**10e** and **10f**) in 70–88% yields. Further, substrates from acyclic ketones also were indiscriminately converted to the corresponding *β*-disubstituted conjugated esters **10g–j** in 60–90% yields. Of note is that the substrates with less acidic 3°-H adjacent to the *tert*-hydroxyl group (**8e–f**, **8j**, and **8l**) were relatively more productive. Substrates from unsymmetrical aliphatic ketones (**8k–8l**) afforded the mixture of diastereomers with the ratio changing along with the steric bias. Significantly, diphenyl substituted adduct **10m** was obtained from **8m** in 58% yield, at relatively lower temperatures (0 °C–rt) which was necessary to avoid some decomposition. Likewise, halosubstituted diphenyl adducts **10n–o** were also obtained, without any obstruction, in moderate yields of 55–62%. Next, mixed ketone (aryl-alkyl) based substrates **8p–r** also reacted smoothly and provided the corresponding products **10p–r**, as a diastereomeric mixture, in moderate yields of 60–65%.

A plausible mechanism for the title reaction is depicted in Scheme 4. Accordingly, activation of electron-rich alkyne (**A**) by an electrophilic iodine reagent might lead to iodoketene oxonium ion **B** which would instantly undergo intramolecular hydroxyl attack to give four membered intermediate **C**. We exclude concerted conversion of **A** to **C** reasoning that the hydroxyl group and *β*-carbon of the alkyne are too long to react unlike in the case of **B** in which the reactive centers fall in closer proximity. The strained ring in **C** will then undergo slow cleavage to deliver the thermodynamic (less sterically hindered *Z*-isomer) product **2** or **6** or **10**.

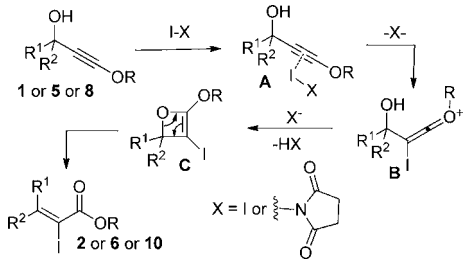
Next, we performed some reactions on products **6a**, **6m**, and **10m** to prove the geometry of the product as well as to extend the importance of the method to the stereodefined synthesis of multiply substituted olefins (Scheme 5). Thus, the reduction of **6a** and **6m** with DIBAL-H in CH_2Cl_2 produced a known conjugated compound **11a**,[9] providing proof for the *Z*-geometry

Scheme 3. Iodo Meyer Schuster Rearrangement of Substrates 8 Prepared from Ketones[a,b]



[a]2 mmol of NIS were added to 1 mmol of **8** in 4 mL of CH_2Cl_2 at rt (0 °C for **8m–o**) and stirred the contents at rt. [b] Isolated yields. [c] The ratio was determined by ^{1}H NMR.

Scheme 4. Proposed Mechanism



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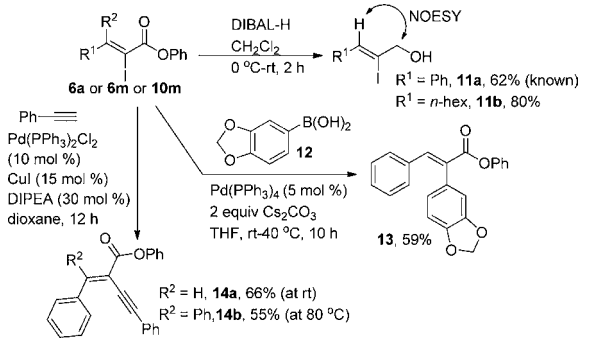
Scheme 5. Utilizations of Functional Groups of α-Iodo Conjugated Ester 6 or 10



of the substrate, and the unknown nonconjugated **11b**. The NOESY spectroscopy of both **11a** and **11b** supported the *Z*-geometry. In fact, ethyl esters **2a**–**f** were known[10] in the literature and spectral data comparison unambiguously established the *Z*-geometry. Next, Suzuki coupling of **5a** with methylenedioxy phenyl boronic acid **12** in the presence of catalytic Pd(0) and 2 equiv of Cs_2CO_3 produced **13** in 59% yield whereas Sonogashira coupling of **6a** and **10m** with phenylacetylene with the assistance of catalytic Pd(II) yielded trisubstituted olefin **14a** and tetrasubstituted olefin **14b** respectively in 55–66% yields.

In summary, an efficient synthesis of linear α-iodo-α,β-unsaturated esters from readily accessible propargylic alcohols is described. This reaction works well not only with substrates derived from aldehydes but also with those from ketones to produce a highly substituted olefin center. *Z*-isomers were exclusively obtained in the case of substrates prepared from aldehydes. Some functional group transformations are performed on few of the products to offer a stereodefined entry to selective tri- and tetrasubstituted olefins.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and copies of ^{1}H and ^{13}C spectra for compounds **2a**–**f**, **5a**–**o**, **6a**–**o**, **8a**–**r**, **9a**–**b**, **10a**–**r**, **11a**–**b**, **13**, and **14a**–**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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