Pergamon

Tetrahedron Letters 40 (1999) 3839–3842

TETRAHEDRON LETTERS

Synthesis of α-iodo-α,β-unsaturated ketones by the reaction of α-silyl-α,β-unsaturated ketones with ICl or ICl-$AlCl_3$

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Received 16 February 1999; accepted 16 March 1999

Abstract

Treatment of α-silyl-α,β-unsaturated enones, readily preparable as regio- and stereodefined compounds in high yields, with either 2 equiv. of ICl or one equiv. each of ICl and $AlCl_3$ provides the corresponding α-iodo-α,β-unsaturated enones in high yields.

Keywords: *α-iodo-α,β-unsaturated ketones, α-silyl-α,β-unsaturated ketones, ICl or ICl-$AlCl_3$, iododesilylation.*

Herein reported are two related procedures for the conversion of α-silyl-α,β-unsaturated enones into the corresponding α-iodo enones under Lewis acidic conditions. Specifically, either one equivalent each of ICl and $AlCl_3$ or two equivalents of ICl can convert α-silyl-α,β-unsaturated enones into the corresponding iodo derivatives typically in ≥80% yields even in cases where the starting α-silyl enones are β-substituted cyclic or acyclic substrates. Coupled with the ready availability of α-silyl-α,β-unsaturated enones by various methods, notably Zr-promoted ene-yne cyclization-carbonylation[1] and Pd-catalyzed acylation[2] of α-silylalkenylmetals, the iodination procedure provides a convenient and attractive route to α-iodo enones.

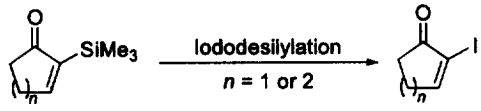
α-Halo-α,β-unsaturated ketones, especially α-iodo derivatives, have become a very important class of compounds for the synthesis of α-substituted enones and their saturated derivatives[3] since the introduction of Pd-catalyzed α-halo enone-based α-substitution methodology in 1991.[4] Virtually all types of carbon groups including aryl, alkenyl, alkynyl, and alkyl groups have been incorporated in the α-position of enones, ketones, and other carbonyl derivatives.[3] Although several reasonably satisfactory procedures for the preparation of α-iodo enones have been developed,[5] they still reveal limitations and difficulties. Moderate to poor yields observed in the preparation of sterically hindered cyclic α-iodo enones and acyclic derivatives, especially (*E*)-α-iodo enones, are some of the notable limitations. One of the most common approaches to the synthesis of α-iodo enones has been to introduce an iodine atom in the α-position of the parent enones.[5a,5b] In many cases, however, their α-silyl-substituted derivatives are more readily available, as demonstrated by the Zr-promoted ene-yne cyclization.[1] It is also noteworthy that both (*E*)- and (*Z*)-α-silylalkenylalanes are often readily accessible in a stereoselective manner by hydroalumination of 1-silyl-1-alkynes.[6] *Syn*-addition of organocoppers[7] and borane-catalyzed *anti*-addition of alkyl iodides[8] to ethynylsilanes also provide selective routes to α-silylalkenylmetals. With these in mind, we sought a convenient and selective route to α-iodo enones *via* α-silyl enones. We therefore prepared several α-silylcyclopentenones by Zr-promoted cyclization-carbonylation[1] and treated them with I_2 and pyridine.[5a] As shown in Table 1, 2-(trimethylsilyl)-2-cyclopentenone (**1**) was converted to the corresponding iodo derivative in 71% yield (Entry 1). However, none of the β-alkyl-substituted enones (**2-4**) gave even traces of the desired iodides (Entries

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00635-8

2-4). A similar dramatic contrast was observed with 2-cyclohexenone derivatives[9] (**5** or **6**) (Entries 5 and 6). Other variants of the I_2-pyridine procedure including that using Me_3SiN_3 as the third reagent[5b] were similarly unsatisfactory in cases where there was an alkyl substituent in the β-position. However, McNelis' procedure[5c] with NIS and PhI(OH)OTs gave 2-iodo-3-methyl-2-cyclopentenone in 52% yield. As this reaction presumably involves iodination under acidic conditions, we explored Lewis acid-catalyzed α-iodination of α-silyl enones for obtaining more favorable results.

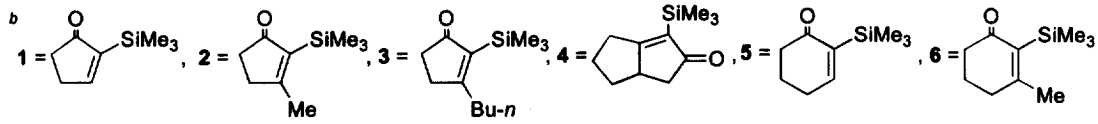
We have indeed found that either one equivalent each of ICl and $AlCl_3$ or two equivalents of ICl[10] is highly satisfactory for conversion of a α-silyl-α,β-unsaturated enones into the corresponding α-iodo derivatives. The experimental results are summarized in Table 1 together with those observed with I_2 and pyridine.

Table 1. Conversion of α-Silyl-α,β-unsaturated Cyclic Enones to α-Iodo-α,β-unsaturated Cyclic Enones.[a]



		Product yields (%)[c]		
Entry	Substrate[b]	observed with ICl (2 equiv.)	observed with ICl/$AlCl_3$	observed with I_2 / pyridine
1	**1**	79	33[d]	71
2	**2**	80	93 (92)	0
3	**3**	80 (80)	44 (42)[e]	0
4	**4**	100 (94)	56 (52)[f]	0
5	**5**	85 (82)	88	84
6	**6**	96	81	0

[a] All experiments were run in CH_2Cl_2 at 0 °C or room temperature in dark. In the reactions with ICl/$AlCl_3$, $AlCl_3$ was placed in a flask. To this were added sequentially an α-silyl enone and a solution of ICl in CH_2Cl_2. ICl from Aldrich was used as received.

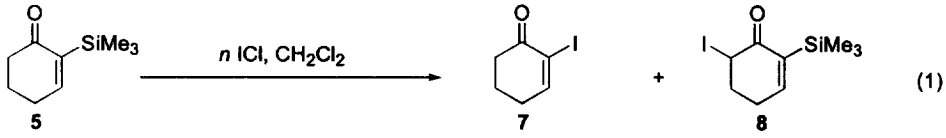
[b] 

[c] NMR yields with isolated yields in parentheses. [d] 50% of unreacted α-silyl ketone recovered. [e] 33% of unreacted α-silyl ketone recovered. [f] 21% of unreacted α-silyl ketone recovered.

The following points are noteworthy. First, two equiv. of ICl in CH_2Cl_2 are satisfactory in all cases examined to date, the yields of the desired products being ≥79%. It should be emphasized that the reaction does require two equiv. of ICl. With just one equiv. of ICl, 2-(trimethylsilyl)-2-cyclohexenone (**5**), for example, was converted to 2-iodo-2-cyclohexenone only in 36% yield even after 24 h at 23 °C with 21% of the starting compound recovered unreacted. Moreover, 2-(trimethylsilyl)-6-iodo-2-cyclohexenone was formed as a byproduct in 31% yield. When only 0.5 equiv. of ICl was used, the desired product was obtained in 7% yield (14% based on ICl) with 43% of the starting compound recovered unchanged, while the above-mentioned byproduct was obtained in 37% yield (74% based on ICl). In sharp contrast, none of the byproduct was formed when 2 equiv. of ICl was used (Eq. 1).

Clearly, the major reaction course changes with the amount of ICl. Although yet to be clarified, one equiv. of ICl appears to be at least initially fully complexed with **5**, and the second equiv. of ICl not strongly complexed with **5** is desirable for observing smooth and high-yield substitution of the Me_3Si group with I. In the absence of

the second equiv. of ICl, slow iodination in the C-6 position becomes faster than the desired formation of **7**. Although we are not yet in a position to propose the detailed mechanisms for these reactions, they must be mechanistically discrete.



5 **7** **8** (1)

n	Temp (°C)	Time (h)	5 (%)	7 (%)	8 (%)
2	0	2	0	88	0
2	0	0.4	46	43	3
1.5	0	0.4	51	31	9
1	0	0.4	51	10	22
1	23	24	21	36	31
0.5	23	24	43	7	37

Table 2. Conversion of α-Silyl-α,β-unsaturated Acyclic Enones to α-Iodo-α,β-unsaturated Acyclic Enones[a]

	Substrate[b]			Conditions		RCH=C(I)COMe	
Entry	R	% *E* or *Z*	Yield[c] (%)	Temp. (°C)	Time (h)	% *E* or *Z*	Yield[d] (%)
1	*n*-Bu	>99% *Z*	65 (65)	0	2	>99% *Z*	85
2	*n*-Bu	90% *E*	80 (76)[e]	0	2	>99% *Z*	98 (83)
3	*n*-Bu	90% *E*	80 (76)[e]	-78	8	69/31 *E/Z*	18[f]
4	*i*-Pr	>99% *E*	70 (52)[g]	0	1	>99% *Z*	73 (65)
5	*i*-Pr	>99% *E*	70 (52)[g]	-78	1	21/79 *E/Z*	85
6	*t*-Bu	>99% *Z*	(64)	0	2	99% *Z*	76 (71)
7	*t*-Bu	>99% *E*	71 (69)	-78	1	98% *E*	67 (67)
8	Ph	93% *Z*	77 (52)	0	2	>99% *Z*	93
9	Ph	97% *E*	85 (85)	0	2	>99% *Z*	100 (99)
10	Ph	97% *E*	85 (85)	-78	0.5	69/31 *E/Z*	100

[a]Typically, the reaction was run with 2 equiv. of ICl in CH_2Cl_2 in dark. [b]Unless otherwise mentioned, the substrates were prepared by treating the corresponding 1-silyl-1-alkynes with *i*-Bu_2AlH either in Et_2O (for the *Z* isomers) or in hexanes (for the *E* isomers) followed by treatment with MeCOCl (3 equiv.) in THF in the presence of 5% of $Pd(dba)_2$. [c]The NMRyields of the substrates based on 1-silyl-1-alkynes NMR yields with isolated yields in parentheses. [d]The yields of α-iodo enones (both stereoisomers). NMR yields with isolated yield in parentheses. [e]After conversion of 1-(trimethylsilyl)-1-hexyne into (*E*)-1-iodo-1-(trimethylsilyl)-1-hexene in 87% yield *via* hydroalumination with *i*-Bu_2AlH in Et_2O and iodinolysis with I_2.[6] successive treatment with *t*-BuLi (2 equiv., -78 to 0 °C, 2 h), $ZnBr_2$, MeCOCl and cat. $Pd(dba)_2$ in THF at 0 °C for 3 h gave the compound as a 9:1 *E/Z* mixture. [f]Observed at 20% conversion with 0.95 equiv. of ICl. [g]Prepared by reacting (trimethylsilyl)acetylene with an organocopper reagent generated *in situ* from *i*-PrMgCl and $LiCuBr_2$[8] followed by treatment with CH_3COCl.

Secondly, a combination of one equivalent each of ICl and $AlCl_3$ is equally satisfactory in most cases, but this reagent system was less effective in the iodination of certain α-silylcyclopentenones primarily due to comparatively low reaction rates (Entries 1,3, and 4). It appears reasonable to propose that $AlCl_3$ activates ICl as a Lewis acid through three-centered $I^{\delta+}$–Cl–$^{\delta-}$Al interaction.[11] A similar mode of activation between two molecules of ICl may also be operating. Thirdly, we also considered protodesilylation of α-silyl enones to convert them first into the desilylated parent enones followed by iodination with I_2 and pyridine as an alternative route. However,

conversion of 3-(*n*-butyl)-2-cyclopentenone into the corresponding α-iodo derivative proceeded only in 19% yield, with roughly 20% of the starting compound recovered unchanged after 24 h, even though the corresponding reaction of 3-methyl-2-cyclopentenone was reported to give the iodinated product in a modest yield of 57%.[5a]

To further extend the scope of the iodination with 2 equiv. of ICl, several representative stereoisomerically ≥90% pure acyclic α-silyl enones were prepared in good to excellent yields mostly by successive treatment of silylated alkynes first with *i*-Bu_2AlH either in Et_2O (for *Z* isomers) or in hexanes (for *E* isomers)[6] and then with acetyl chloride in the presence of 5 mol% of $Pd(dba)_2$ in THF[2] followed by basic workup (NaOH) avoiding acid formation. These α-silyl enones were treated with 2 equiv. of ICl in CH_2Cl_2 at 0 or -78 °C. The results sumarized in Table 2 indicate the following. At 0 °C, all substrates gave stereoisomerically ≥99% pure (*Z*)-α-iodo enones in good yields (Entries 1,2,4,6,8, and 9). Thus, the reaction is highly stereoselective but stereoconvergent under these conditions. On the other hand, the reaction can be stereospecific under kinetically controlled conditions. Thus, (*E*)-3-(trimethylsilyl)-5,5-dimethyl-3-hexen-2-one was converted to 98% pure *E*-isomer of the corresponding iodide in 67% yield. Synthesis of acyclic (*E*)-α-iodo enones of high stereoisomeric purity without isomeric separation[12] appears to be unprecedented. Unfortunately, however, the rate of *E*-to-*Z* isomerization induced by ICl was too fast even at -78 °C to allow the preparation of (*E*)-α-iodo enones in cases where the β-substituent is *n*-Bu (*E*/*Z* = 2 at 20% conversion) and Ph (*E*/*Z* = 2).

Acknowledgments. We thank the National Institutes of Health (GM 36792) and Purdue University for support of this research.

References

(1) (a) Negishi E, Holmes SJ, Tour JM, Miller JA. J. Am. Chem. Soc. 1985;107:2568. (b) Negishi E, Cederbaum FE, Takahashi T. Tetrahedron Lett. 1986;27:2829. (c) Negishi E, Holmes SJ, Tour JM, Miller JA, Cederbaum FE, Swanson DR, Takahashi T. J. Am. Chem. Soc. 1989;111:3336. (d) Takahashi T, Xi Z, Nishihara Y, Huo S, Kasai K, Aoyagi, K, Denisov V, Negishi E. Tetrahedron 1997;53:9123.

(2) Negishi E, Bagheri V, Chatterjee S, Luo FT, Miller JA, Stoll AT. Tetrahedron Lett. 1983;24:5181.

(3) For a review, see Negishi E. J. Organomet. Chem. in press.

(4) Negishi E, Owczarczyk Z, Swanson DR. Tetrahedron Lett. 1991;32:4453.

(5) For representative procedures, see the following papers and those cited therein: (a) Johnson CR, Adams JP, Braun MP, Senanayake CBW, Wovkulich PM, Uskokovič MR. Tetrahedron Lett. 1992;33:917. (b) Sha CK, Huang SJ. Tetrahedron Lett. 1995;36:6927. (c) Angara GJ, McNelis E. Tetrahedron Lett. 1991;32:2099. (d) Bellina F, Carpita A, Ciucci D, De Santis M, Rossi R. Tetrahedron 1993;49:4677. (e) Djuardi E, Bovonsombat P, McNelis E. Synth. Comm. 1997;24:2497

(6) (a) Eisch JJ, Foxton MW. J. Org. Chem. 1971;36:3520. (b) Zweifel G, Lewis W. J. Org. Chem. 1978;43:2739. (c) Zweifel G, Miller JA. Organic Reactions 1984;32:375.

(7) (a) Obayashi M, Utimoto K, Nozaki H. Tetrahedron Lett. 1977:1805. (b) Westmijze H, Kleijn H, Vermeer P. J. Organomet. Chem. 1984;276:317.

(8) Ichinose Y, Matsunaga S, Fugami K, Oshima K, Utimoto K. Tetrahedron Lett. 1989;30:3155.

(9) Prepared by lithiation with *n*-BuLi, silylation, and deprotection of the corresponding ethylene glycol-protected α-bromocyclohexenones; Shih C, Fritzen EL, Swenton JS. J. Org. Chem. 1980;45:4462.

(10) (a) For conversion of one heteroaromatic silylated indolizinone into the iodo derivative with ICl, see Earl RA, Vollhardt KPC. J. Org. Chem. 1984;49:4786. (b) For conversion of silylbenzoquinones into the iodo derivatives with ICl, see Chan KS, Mak CC. Tetrahedron 1994;50:2003.

(11) Negishi E. Chem. Eur. J. 1999;5:411.

(12) For a synthesis of stereoisomeric mixtures of α-iodo enones in which the *E*/*Z* ratio is ca. 3, see Ref. 5d.