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Synthesis of 2-iodoynamides and regioselective [2+2] cycloadditions with ketene

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Dedicated to Professor Harry Wasserman in recognition of his contributions to the science of organic synthesis and his outstanding record of leadership and service to the chemistry community

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ABSTRACT

The first synthesis of 2-iodoynamides is described as well as the first [2+2] cycloadditions of ketene with iodo alkynes.

1. Introduction

In a now classic 1962 publication in *Tetrahedron Letters*, Wasserman and Dehmlow reported the first systematic investigation of the reaction of ketenes with alkynyl ethers.[1,2] A subsequent full paper[3] expanded on this study, and described a number of interesting transformations of the 3-alkoxycyclobutenone cycloadducts including reactions with Grignard reagents to afford 3-alkyl and 3-arylcyclobutenones. This latter transformation is of some significance since it provides access to cyclobutenones that are not available via direct [2+2] cycloadditions of ketenes with alkyl- and aryl-substituted acetylenes. Unactivated alkynes only engage in efficient cycloadditions with highly electrophilic ketenes such as dichloroketene,[4] and simple ketenes require electron-rich, heterosubstituted alkynes for efficient reaction.[5]

Ynamines[6] comprise another class of heterosubstituted alkynes that react with ketenes in [2+2] cycloadditions.[7] Unfortunately, these reactions often lead to mixtures of the desired cyclobutenones accompanied by allenyl amides.[8] The formation of the allene byproducts is believed to result from initial addition of the ynamine across the ketene carbonyl group via a stepwise pathway to form an alkylideneoxete. Electrocyclic ring opening then transforms this strained intermediate to the allenyl carboxamide. However, *ynamides*, in which the nucleophilicity of the amino alkyne is attenuated by the electron-withdrawing substituent on the nitrogen atom, do react smoothly with a variety of ketenes to afford 3-aminocyclobutenone derivatives in good yield.[9]

Cyclobutenones are valuable synthetic intermediates that participate in a variety of novel and useful synthetic transformations.[10] In connection with our work on benzannulation strategies based on the reaction of alkynes with aryl- and vinylketenes,[11] we became interested in the synthesis of 2-iodoynamides and the question of whether they can function as efficient ketenophiles in [2+2] cycloadditions. At the outset of this study the feasibility of these cycloadditions was far from certain. To our knowledge, no successful example of the cycloaddition of a ketene and alkynyl halide had been reported previously. In fact, in the case of halo-substituted alkenes, we were aware of only a single example of a ketene [2+2] cycloaddition, the low-yield reaction of bis(trifluoromethyl) ketene with methyl trifluorovinyl ether.[12,13] Herein we report the first syntheses of 2-iodoynamides and the finding that these acetylenes participate in remarkably efficient [2+2] cycloadditions with ketene.

2. Preparation of iodo alkynes

For the preparation of the iodo alkynes used in this study we focused our attention on the iodination of alkynyllithium compounds, an approach that has previously proved efficacious for the synthesis of simple alkynyl iodides[14] and 2-iodo-1-alkoxyacetylenes.[15] In this fashion, 1-iodooctyne was prepared in quantitative

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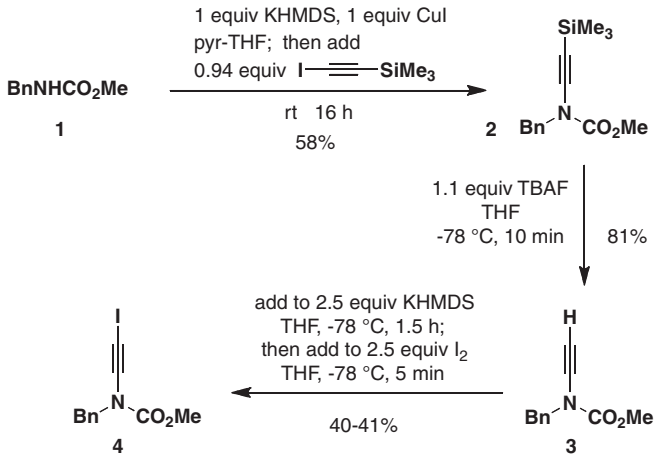
yield by reaction of octynyllithium with 1.05 equiv of I_2 in THF (−78 °C to rt, 1.5 h), and iodoethoxyacetylene was generated in good yield (as previously reported by Vermeer[15a]) and used without purification due to its instability.

In recent years ynamides have emerged as exceptionally useful building blocks for organic synthesis.[16] Considerably more robust than simple ynamines, ynamides are more easily stored and handled, and more resistant to hydrolysis and polymerization. Ynamides tolerate a variety of reaction conditions incompatible with simple ynamines and have thus proved to be versatile substrates for a variety of synthetic transformations. To our knowledge, however, no examples of 2-halo ynamides have been reported previously.

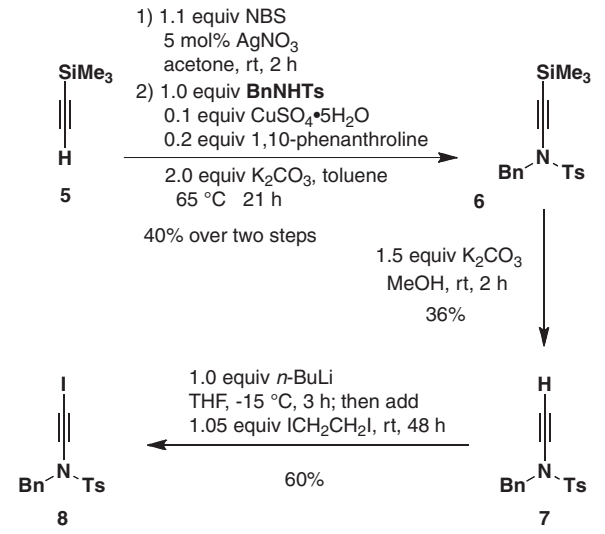
Not surprisingly, initial attempts to prepare 2-iodoynamides via the reaction of terminal ynamides with NIS in the presence of catalytic silver nitrate did not appear promising, and so we have focused most of our attention on reactions of metalated ynamides with mild iodinating agents such as molecular iodine and 1,2-diiodoethane. The requisite terminal ynamides for metalation are conveniently prepared via the N-alkynylation of carboxamides and sulfonamides using (trialkylsilyl)alkynyl halides followed by protodesilylation.

Recent advances in our laboratory[17] and that of Hsung[18] have provided the basis for the efficient and convenient synthesis of a variety of ynamides. We have found these methods to be complementary, and both procedures were employed in the present study. Although the protocol developed in our laboratory requires the use of 1 equiv of CuI, coupling proceeds smoothly at room temperature and this method thus accommodates the synthesis of a wide range of alkyne derivatives including thermally unstable systems. Hsung's related protocol employs catalytic CuCN or $CuSO_4$ in conjunction with diamine ligands and requires reaction at elevated temperatures. We have found both methods to be reliable and reproducible for reactions on both small and large (i.e., multigram) scale.

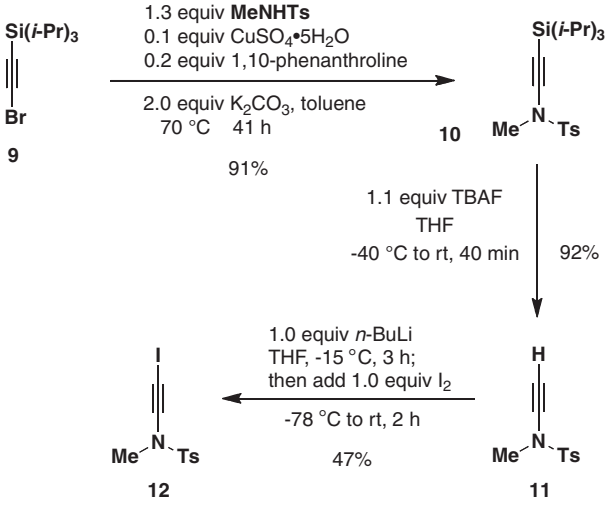
Scheme 1 outlines the synthesis of the 2-iodoynamide **4**. Alkynylation of carbamate **1**[19] with iodo(trimethylsilyl)acetylene[20] afforded ynamide **2**,[21] which underwent smooth protodesilylation on exposure to TBAF at −78 °C.[22] Initial attempts to deprotonate **3** with KHMDS led to complex mixtures, possibly triggered by addition of the acetylide to the carbamate carbonyl group. Improved results were obtained by slow addition (1.5 h) of the ynamide to a solution of excess base in THF at −78 °C. Cannulation of the resulting solution into a solution of 2.5 equiv of iodine in THF at −78 °C then led to rapid formation of the desired alkynyl iodide **4** which was isolated after column chromatography on acetone-deactivated silica gel as a pale orange solid, mp 56–58 °C. The spectroscopic data for **4** was fully consistent with the assigned structure, including in particular the dramatic upshield shift of the C-2 carbon to −13.3 ppm in the ^{13}C NMR spectrum due to the large diamagnetic shielding by the iodine atom ('heavy atom effect').[23]



Scheme 1.



Scheme 2.



Scheme 3.

Schemes 2 and 3 describe syntheses of the related *N*-sulfonyl iodoynamides **8** and **12**. Witulski and Stengel have previously reported the synthesis of ynamide **7** via an N-alkynylation protocol based on phenyl(trimethylsilylethynyl)iodonium triflate;[24] we found it more convenient to access this ynamide via the copper-catalyzed N-alkynylation of readily available bromo(trimethylsilyl)acetylene.[25] Surprisingly, reaction of **7** with either KHMDS or *n*-butyllithium followed by addition of iodine failed to afford any of the desired iodoynamide. However, in this case formation of **8** in good yield could be achieved by employing 1,2-diiodoethane as the iodinating agent. The desired ynamide **8**, mp 89–93 °C, was obtained in 60% yield after low-temperature recrystallization from ether/pentane.[23]

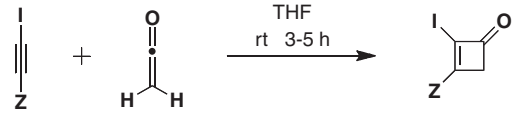
The preparation of iodoynamide **12** proceeded in a similar fashion beginning with the known bromo alkyne **9**.[26] In this case, iodination with molecular iodine was successful and afforded iodoynamide **12** as colorless crystals, mp 95–98 °C, after recrystallization at −20 °C from ether/pentane.[23]

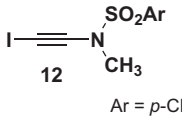
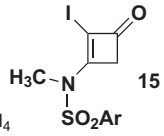
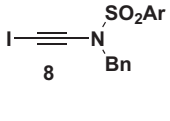
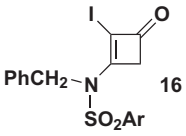
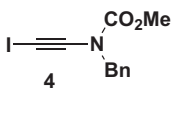
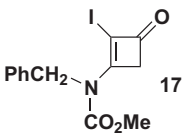
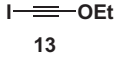
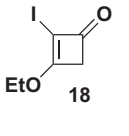
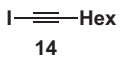
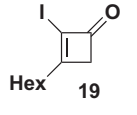
Iodoynamides **4**, **8**, and **12** proved to be relatively stable compounds, and can be stored for weeks as solutions in dichloromethane below 0 °C without noticeable decomposition. Though somewhat sensitive to silica gel, column chromatography can be carried out without significant losses by employing triethylamine-deactivated silica gel.

3. [2+2] cycloadditions

With efficient routes to the requisite iodo alkynes in hand, we turned our attention to examining the feasibility of their [2+2] cycloadditions with ketene. For these reactions, ketene was generated by pyrolysis of acetone in a Hurd 'ketene lamp' as described previously[27] and bubbled into a 0.05–0.1 M solution of the ynamide in THF.[28] Table 1 summarizes our results. The reaction of iodo ynamide **12** with ketene was examined first. Complete consumption of alkyne was observed after 4 h and a single crystalline cyclobutenone was formed which was isolated in 86% yield after purification by silica gel chromatography followed by recrystallization from acetonitrile at −20 °C.[29] A heteronuclear multiple bond correlation (HMBC) experiment permitted assignment of the regiochemistry of the cycloadduct to be that of cyclobutenone **15** in which the nitrogen substituent is attached at the C-3 carbon and the iodine at C-2.[30,31] Ynamides **4** and **8** react with ketene with similar efficiency, but cycloadditions with the alkynyl ether **13** and iodooctyne were not successful. In the case of **13**, complete consumption

Table 1
[2+2] cycloadditions of iodo alkynes with ketene



Entry	Alkyne	Cycloadduct	Yield[a] (%)
1			86
2			81
3			99
4			0
5			0[b]

[a]Isolated yields of products purified by column chromatography.
[b]Reaction was run for 39 h. Unreacted iodooctyne was isolated in 78% yield after column chromatography.

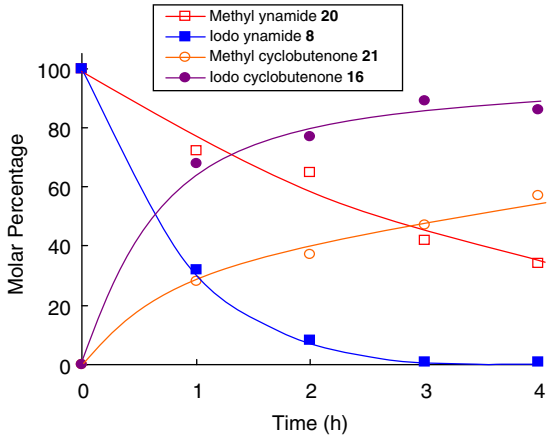
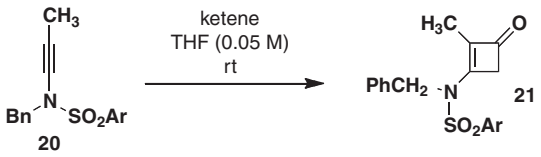


Figure 1. Comparison of rate of [2+2] cycloaddition of ketene with iodoynamide **8** and propynylynamide **20**.



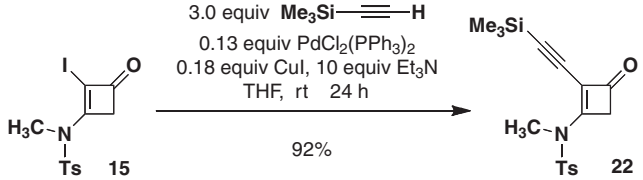
Scheme 4.

of the alkynyl ether occurred within 3 h, but no cyclobutenone cycloadduct could be detected in the resulting complex mixture. Bubbling ketene into a solution of iodooctyne for 39 h failed to produce any cycloadduct, and unreacted alkynyl iodide was recovered in 78% yield after chromatography.

The enhanced reactivity of the iodo ynamides **4**, **8**, and **12** relative to iodooctyne is expected due to the activating effect of the electron-donating nitrogen substituent in ketene cycloadditions. The failure of the iodo alkynyl ether **13** to afford cyclobutenone is attributed to the relative instability of this sensitive alkyne. With regard to the effect of the iodine substituent on the reactivity of the acetylenes, a comparison of the rate of the reactions of iodoynamide **8** and terminal ynamide **7** indicated that the iodine substituent is somewhat deactivating relative to hydrogen. Interestingly, however, iodoynamide **8** reacts more rapidly as compared to the propynyl ynamide **20** which bears a methyl group at C-2 in place of iodine. Figure 1 compares the rates of the reaction of **8** with ketene with the cycloaddition of **20** (Scheme 4) run as a separate parallel reaction.[32] Reaction of the iodoynamide is complete in ca. 2 h, while at 3 h only ca. 50% of the propyne derivative was found to have reacted.

4. Synthetic utility of the cycloadducts

Cross-coupling of the 2-iodocyclobutenones produced in these reactions should provide the basis for their elaboration to cyclobutenones bearing a variety of other substituents. For example, Sonogashira coupling of **15** with (trimethylsilyl)acetylene affords the expected 2-alkynylcyclobutenone in 92% yield (Scheme 5).



Scheme 5.

Further studies are underway in our laboratory to investigate the synthetic utility of 2-iodoynamides including, in particular, their participation as novel ketenophile components in benzannulation reactions with vinyl- and arylketenes.

Acknowledgments

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Supplementary data

Supplementary data (proton and carbon NMR spectra for iodoynamides and cyclobutenones) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.11.002.

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23. *Characterization data for iodoynamides*: For **4**: mp 56–58 °C; IR (neat) 2955, 2200, 1712, 1446, 1367, 1261, 1116, 942, 759, and 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30-7.41 (m, 5H), 4.63 (s, 2H), and 3.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8, 135.9, 128.8, 128.5, 128.4, 83.7, 54.5, 53.7, and −13.3; HRMS-DART m/z $[M+H]^+$ calcd for $C_{11}H_{10}INO_2$, 315.9829; found 315.9835. For **8**: mp 89–93 °C; IR (neat) 3032, 2188, 1597, 1496, 1455, 1363, 1169, 1088, and 601 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, J = 8.5 Hz, 2H), 7.24–7.35 (m, 7H), 4.50 (s, 2H), and 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.0, 134.8, 134.4, 130.0, 128.9, 128.7, 128.6, 127.9, 83.5, 55.4, 21.9, and −12.5; HRMS-ESI $[M+Na]^+$ calcd for $C_{16}H_{14}INO_2S$, 433.9682; found 433.9672. For **12**: mp 95–98 °C; IR (neat) 2936, 2186, 1363, 1170, 1088, 978, and 715 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 3.07 (s, 3H), and 2.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.2, 133.3, 130.1, 128.0, 84.7, 38.9, 21.9, and −14.5; HRMS-DART m/z $[M+H]^+$ calcd for $C_{10}H_{10}INO_2S$, 335.9550; found 335.9565.
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25. Prepared from (trimethylsilyl)acetylene by reaction with NBS and catalytic $AgNO_3$ according to the method of Hofmeister, H.; Annen, K.; Laurent, H.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 727.
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28. Reaction at higher concentration led to precipitation of the cyclobutenone product and clogging at the outlet of the needle in the reaction mixture.
29. *Representative procedure*: Ketene was generated by pyrolysis of acetone over an electrically heated metal filament using the apparatus described by Williams and Hurd. A 20-mL test tube equipped with a stir bar, rubber septum, and argon inlet needle was charged with iodo ynamide **12** (0.188 g, 0.560 mmol) and 11.2 mL of THF. The argon inlet needle was replaced with a 15-gauge needle connected via Tygon tubing to the ketene generator. The septum was fitted with an outlet needle connected via tubing to a column of $CaSO_4$ leading to a trap of H_2O. Ketene was bubbled into the pale yellow reaction mixture with vigorous stirring at rt over a period of 4 h. The resulting brown solution was then concentrated to afford 0.308 g of a brown solid. Column chromatography on 20 g of silica gel (gradient elution with 15–55% EtOAc–hexanes) afforded 0.200 g of an off-white solid. Recrystallization from 3 mL of CH_3CN at −20 °C furnished 0.181 g (86%) of cyclobutenone **15** as colorless needles.
30. Strong J-coupling was observed between the alkene carbon bearing the nitrogen substituent and the C-4 methylene protons. Strong coupling was also observed between the C-1 carbonyl carbon and these protons. Only weak coupling of the alkene carbon bearing iodine to the methylene protons was noted.
31. *Characterization data for cyclobutenones*: For **15**: mp 160 °C (dec); IR (neat) 2924, 1781, 1757, 1563, 1405, 1371, 1162, 1003, and 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 3.80 (s, 2H), 3.64 (s, 3H), and 2.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.6, 166.7, 146.3, 134.4, 130.8, 127.7, 57.1, 51.5, 35.8, and 21.9; HRMS-DART m/z $[M+H]^+$ calcd for $C_{12}H_{12}INO_3S$, 377.9655; found 377.9639. For **16**: IR (neat) 3064, 3033, 2928, 1763, 1557, 1373, 1319, 1172, and 1048 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, J = 8.5 Hz, 2H), 7.29–7.36 (m, 3H), 7.20–7.28 (m, 4H), 5.36 (s, 2H), 3.82 (s, 2H), and 2.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.2, 166.6, 146.0, 135.4, 135.0, 130.3, 129.0, 128.3, 127.9, 127.6, 57.9, 51.5, 51.4, and 21.8; HRMS-DART m/z $[M+H]^+$ calcd for $C_{18}H_{16}INO_3S$, 453.9968; found 453.9959. For **17**: IR (neat) 3032, 2956, 1767, 1746, 1573, 1449, 1353, 1223, 1113, and 1040 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27–7.40 (m, 5H), 5.27 (s, 2H), 3.89 (s, 2H), and 3.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.5, 168.3, 153.2, 136.0, 129.0, 128.2, 127.0, 59.2, 54.9, 52.1, and 50.0; HRMS-DART m/z $[M+H]^+$ calcd for $C_{13}H_{12}INO_3$, 357.9935; found 357.9922.
32. Solutions of each ynamide (0.20 mmol) in THF (4 mL) containing 1,4-dimethoxybenzene (0.20 mmol) as internal standard were simultaneously treated with ketene which was generated as described above[29] and then split into two streams prior to introduction into the reaction mixtures. Aliquots were analyzed by ^1H NMR spectroscopy (500 MHz, $CDCl_3$) at 1-h intervals to determine the concentration of ynamide and cyclobutenone versus the internal standard.