Reactions of Carbonyl-Conjugated Alkynes with *N*-Bromosuccinimide and *N*-Iodosuccinimide in DMF/H_2O and Methanol/Sulfuric Acid: Syntheses of Dihalo Diketones, Dihalo Ketoesters, and Dihalo Acetals†

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The following terminal, carbonyl-conjugated alkynes were reacted with *N*-bromosuccinimide (NBS) and *N*-iodosuccinimide (NIS) in MeOH/H_2SO_4 to give dibromo and diiodo acetals in the indicated yields: 3-butyn-2-one, **1**: NBS (75%), NIS (95%); 1-phenyl-1-propyn-1-one, **2**: NBS (90%), NIS (40%); 1-hexyn-3-one, **3**: NBS (90%), NIS (70%); methyl propiolate, **4**: NBS (20%, not isolated), NIS (95%). 4,4-Dimethyl-1-pentyn-3-one (**5**) gave only a trace of dibromo acetal and no diiodo acetal; tribromide and tetrabromide were the major products. NBS and NIS reactions required, respectively, 20% and 33 wt % of H_2SO_4. The reaction was unsuccessful with internal alkynes 4-phenyl-3-butyn-2-one and 3-hexyn-2-one which gave only complex mixtures of products. Alkyne **2** gave a significant yield of acetal-ketal in addition to the dihalo acetals. Both the dibromo acetal-ketal and diiodo acetal-ketal were isolated, but only the former could be hydrolyzed to the dibromo acetal. Internal, carbonyl-conjugated alkynes reacted with NBS and NIS in H_2O/DMF (40:60) to give the following products in the indicated yields: 4-phenyl-3-butyn-2-one (**6**): 1-phenyl-3,3-dibromo-1,3-butanedione (**17**, 70%), 1-phenyl-3,3-diiodo-1,3-butanedione (**21**, 95%); 3-hexyn-2-one (**7**): 3,3-dibromo-2,4-hexanedione (**18**, 80%), 3,3-diiodo-2,4-hexanedione (**22**, 95%); methyl 3-phenyl-2-propynoate (**8**): methyl 2,2-dibromo-3-keto-3-phenylpropanoate (**19**, 43%), methyl 2,2-diiodo-3-keto-3-phenylpropanoate (**23**, 95%); methyl 2-pentynoate (**9**): methyl 2,2-dibromo-3-ketopentanoate (**20**, 80%), methyl 2,2-diiodo-3-ketopentanoate (**24**, 95%). All reactions, except for **6** and **8** with NBS, required H_2SO_4. The terminal, carbonyl-conjugated alkyne, 3-butyn-2-one, did not give products, possibly because of oxidation of the intermediate aldehyde by NBS and NIS. Mechanisms involving electrophilic attack by halogen on the triple bond and an acid-catalyzed mechanism are discussed.

In a continuation of our studies on the reactions of α,β-unsaturated ketones and esters with halogens and *N*-halosuccinimides in nucleophilic solvents,[1−3] we decided to investigate the reactions of carbonyl-conjugated alkynes with NBS and NIS in H_2O/DMF and in methanol (MeOH), catalyzed by H_2SO_4, as potential syntheses of dihalo diketones/dihalo ketoesters and dihalo acetals, respectively. Previously, we showed that methoxy bromides could be synthesized from the reaction of α,β-unsaturated alkenic ketones and esters with NBS in MeOH and H_2SO_4.[3] We suspected that the carbonyl-conjugated alkynes, because of lower reactivities, would also require acid catalysis. No previous studies on the less reactive carbonyl-conjugated alkynes with halogen systems in nucleophilic solvents have been undertaken. Several years ago, it was shown that three alkynes (not carbonyl-conjugated) reacted with NBS in H_2O/DMF to give dibromo ketones in good yield.[4] Dichlorodimethyl ketals (acetals were not reported) have been prepared by the reaction of alkynes (not carbonyl-conjugated) with *N*-chlorosuccinimide (NCS) in MeOH.[5]

Results and Discussion

Reactants, conditions, products, and yields for the reactions of several terminal carbonyl-conjugated alkynes with NBS/NIS in MeOH/H_2SO_4 and internal carbonyl-conjugated alkynes with NBS/NIS in H_2O/DMF, and H_2SO_4 in certain cases, are summarized in Tables 1 and 2, respectively. All products were characterized with ^{1}H NMR, ^{13}C NMR, and IR. Furthermore, the structures of all products were confirmed by one or more of the following: high-resolution mass spectrometry, reduction to known compounds with tributyltin hydride and, in the case of **17**, by literature data. Low resolution mass

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(1) Heasley, V. L.; Elliott, S. L.; Erdman, P. E.; Figueroa, D. E.; Krosley, K. K.; Louie, T. J.; Moore, H. B.; Mudge, B. P.; Nogales, D. F.; Nordeen, J.; Oakes, M. E.; Rosbrugh, Jr., J. W.; Sauerbrey, A. M.; Shibuya, T. Y.; Stanley, M. S.; Stewart, C. C.; Shellhamer, D. F.; Heasley, G. E. *J. Chem. Soc., Perkin Trans. 2* **1991**, 393.

(2) Heasley, V. L.; Louie, T. J.; Luttrull, D. K.; Millar, M. D.; Moore, H. B.; Nogales, D. F.; Sauerbrey, A. M.; Shevel, A. B.; Shibuya, T. Y.; Stanley, M. S.; Shellhamer, D. F.; Heasley, G. E. *J. Org. Chem.* **1988**, *53*, 2199.

(3) Heasley, V. L.; Wade, K. E.; Aucoin, T. G.; Gipe, D. E.; Shellhamer, D. F.; Heasley, G. E. *J. Org. Chem.* **1983**, *48*, 1377.

(4) Mitsev, I. D.; Panaiotova, B. D.; Iovchev, A. L.; Khristova, N. I. *Dokl. Bolg. Akad. Nauk.* **1974**, *27*, 1403.

(5) Reed, Jr., S. F. *J. Org. Chem.* **1965**, *30*, 2195.

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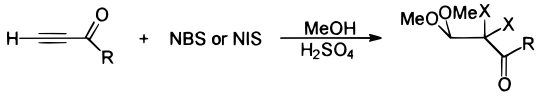
Table 1. Syntheses of Dihalo Acetals



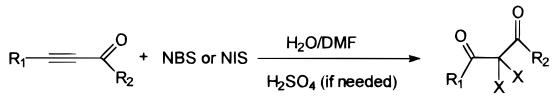
Alkynes: **1** - **4**

Dibromides: **10** - **12**
Diiodides: **13** - **16**

		H_2SO_4 (%)[a]		acetal, yield (%)	
alkyne	R	NBS	NIS	NBS	NIS
1	Me	20	33	**10** (75)	**13** (95)
2	Ph	20	33	**11** (90)	**14** (40)
3	Pr	20	33	**12** (90)	**15** (70)
4	OMe	*b*	33	*b*	**16** (95)

[a] H_2SO_4 is percent by weight of DMF, H_2O, and H_2SO_4. [b] Yield was low (20%); product was not isolated.

Table 2. Syntheses of Dihalo Diketones and Dihalo Ketoesters



Alkynes: **1**-**4**

X = Br for dibromides **17**-**20**
X = I for diiodides **21**-**24**

		H_2SO_4 (%)[a]		dihalo diketone/ dihalo ketoester, yield (%)	
alkyne	R_1, R_2	NBS	NIS	NBS	NIS
6	R_1 = Ph, R_2 = Me	0	12	**17** (70)	**21** (95)
7	R_1 = Et; R_2 = Me	8	12	**18** (80)	**22** (95)
8	R_1 = Ph, R_2 = OMe	0	20	**19** (43)	**23** (95)
9	R_1 = Et, R_2 = OMe	15	20	**20** (80)	**24** (95)

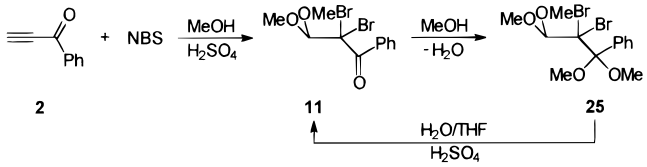
[a] H_2SO_4 is percent by weight of DMF, H_2O, and H_2SO_4.

spectra were obtained for many of the compounds. Elemental analyses were not attempted on any of the products because of their instabilities. Only one of the products (**17**) from either synthetic procedure has been reported previously. Yields were determined by NMR using internal standards. CH_2Cl_2: **10**, **11**, **12**, **14**, **17**, **19**, **21**, **22**, **23**, **24**; C_6H_6: **13**, **15**, **16**, **18**, **20**. Preliminary examination showed that NCS with terminal alkynes in MeOH/H_2SO_4 failed to give products. NCS reacted with **6**, an internal alkyne, in H_2O/DMF to give a product suspected of being 1-phenyl-3,3-dichloro-1,2-butanedione, but the reaction failed with **7**.

As shown in Table 1, terminal alkynes 3-butyn-2-one (**1**), 1-phenyl-2-propyn-1-one (**2**), and 1-hexyn-3-one (**3**) gave acceptable yields of dibromo and diiodo acetals. The regiochemistry of our products (acetals) is the opposite of the products (ketals) in the earlier study with NCS and terminal alkynes.[5] High concentrations of sulfuric acid were definitely required. In the presence of lower amounts of acid (10−15% H_2SO_4), vinyl dihaloketones were the major products with both NBS and NIS. Apparently, with less acid, decomposition occurs to give Br_2 and I_2 which add to the alkyne. Methyl propiolate (**4**) produced the dibromo acetal in low yield (∼20% by GC) which was confirmed by GC-MS but could not be isolated. Only a trace of dibromo acetal could be detected in the reaction of 4,4-dimethyl-1-pentyn-3-one (**5**) with NBS. The major products were tribromide and tetrabromide. We have no explanation for the fact that **5** failed to react like the other alkynes. NIS and **5** in MeOH/H_2SO_4 gave a complex mixture which was not resolved. Vinyl dihaloketones always accompanied the dihalo acetals as minor byproducts. They were identified by GC/MS but were not isolated. Dibromo acetals were purified by chromatography (hexane/ether, 1−2%). Diiodo acetals were isolated crude in high purity but could not be purified because of decomposition during recrystallization or chromatography over silica. Solutions of the diiodo acetals rapidly turned purple. The purities of the dibromo and diiodo acetals were confirmed by their ^1H and ^{13}C NMR spectra; the purities (>90%) of the dibromo acetals were also confirmed by reverse-phase HPLC (acetonitrile/H_2O).

Internal alkynes 4-phenyl-3-butyn-2-one (**6**) and 3-hexyn-2-one (**7**) were investigated with both NBS and NIS in MeOH, with varying amounts of acid, but without success. With NBS, low yields of dibromo ketal, vinyl dibromoketones, and many other byproducts were observed by GC and GC-MS. NIS yielded no identifiable products. 1-Hexyne, a non-carbonyl-conjugated alkyne, reacted with NBS in MeOH/H_2SO_4 to give the ketal, 1,1-dibromo-2-hexanone, and vinyl dibromide, suggesting that the carbonyl group is required for terminal acetal formation.

Alkyne (**2**) reacted with NBS in MeOH/H_2SO_4 to form an acetal-ketal (**25**) in addition to dibromo acetal (**11**). Acetal-ketal **25** was isolated and hydrolyzed to **11**:

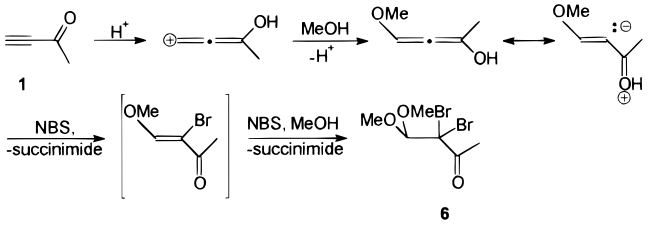


2 **11** **25**

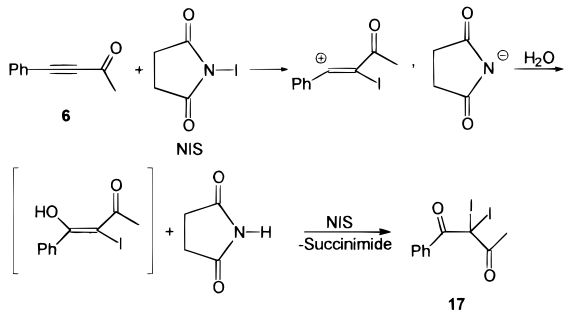
NIS and **2** in MeOH/H_2SO_4 also gave both diiodo acetal **14** and diiodo acetal-ketal **26**, but **26** could not be hydrolyzed to **14**. Alkynes **1** and **3** and NBS also formed small amounts of acetal-ketals which were identified by their mass spectra.

The data in Table 2 show that internal alkynes 4-phenyl-3-butyn-2-one (**6**), 3-hexyn-2-one (**7**), methyl 3-phenyl-2-propynoate (**8**), and methyl 2-pentynoate (**9**) gave dihalo ketones and dihalo ketoesters in good yield. Vinyl dihaloketones and dihaloketoesters were formed as minor byproducts and were identified by GC/MS but not isolated. Dibromo diketones and ketoesters were purified by chromatography (hexane/ether, 1−2%). The diiodo ketones were isolated in high purity at the end of the workup but, with the exceptions of **21** and **23**, which were recrystallized from hexane, could not be purified further because of decomposition during distillation, recrystallization, or chromatography, as indicated by the extensive formation of iodine. The purities of the dihalo diketones and dihalo ketoesters were confirmed by their ^1H and ^{13}C NMR spectra. All of the internal alkynes reacted slowly with NIS without acid catalysis, but significant byproducts were formed in the absence of acid, and the reactions did not go to completion. With acid in high concentration, NIS and the alkynes reacted rapidly, leading to very pure products (ca. 95%). NBS is apparently less reactive than NIS since acid is required for a reaction to occur with NBS and alkynes **7** and **9**. Reaction of terminal alkyne 3-butyn-2-one (**1**) with either NBS or NIS in DMF/H_2O did not lead to products. We suspect that a dihalo aldehyde may have formed initially and then was oxidized further, perhaps to a carboxylic acid. To test this hypothesis, we determined that an aldehyde, pentanal, disappeared rapidly, probably by oxidation with NBS.

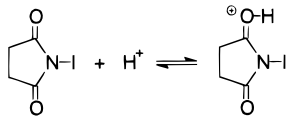
Because of the requirement for strong acid, we speculate that an acid-catalyzed mechanism, as reported previously[1−3] for alkenes, is involved in the reaction of the terminal alkynes with NBS and NIS. The following reactions illustrate this mechanism using 3-butyn-2-one (**1**) and NBS:



Apparently, NIS is sufficiently reactive to deliver "I^+" to the π-bond of the internal alkynes, as shown below with **6**, leading to an intermediate enol which reacts rapidly with a second NIS, producing the diiodo diketones:[6]



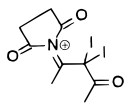
Acid may increase the rate of the reaction by protonating the oxygen in NIS, leading to a more reactive iodinating agent:



NBS is also able to deliver "$Br^{\oplus}$" to alkynes **6** and **8**, probably because of the stabilities of the phenyl-substituted cation intermediates; a mechanism like that described for **6** and NIS is likely involved. Protonated NBS, as discussed with NIS, probably accounts for the increase in reactivity of NBS with acid. Conceivably, the increase in the rates of reaction of NIS and NBS in the presence of acid occurs via the acid-catalyzed mechanism described above for terminal alkynes.

The fact that only one of the two possible isomers is formed with the internal alkynes may be explained by assuming that the charge in the intermediate cation is localized on the β-carbon because of stabilization by the phenyl ring or ethyl group. Positive charge would not be anticipated on the α-carbon because of proximity to the carbonyl group. On the other hand, in those reactions involving acid, formation of only one regioisomer may be a consequence of the acid-catalyzed mechanism described above with the terminal alkynes.

(6) A reviewer has pointed out that our data are consistent with an enamide intermediate (see structure), perhaps accounting for the regiochemistry and the difference in reactivity between NBS and NIS. An enamide intermediate is also compatible with the acid-catalyzed mechanism. We have no evidence to support the formation of this intermediate.



(7) Moriarity, R. M.; Vaid, R. K.; Farid, P. *J. Chem. Soc., Chem. Commun.* **1987**, 711.

Experimental Section

Materials. 3-Butyn-2-one (**1**), methyl propiolate (**4**), and 4-phenyl-3-butyn-2-one (**6**) were obtained from Aldrich; 3-hexyn-2-one (**7**) was purchased from Farchan Laboratories. Methyl 3-phenyl-2-propynoate (**8**) was prepared by refluxing overnight 3-phenylpropiolic acid (Aldrich, 1 g, 6.8 mmol) in 10 mL of MeOH containing 0.5 mL of BF_3 etherate, followed by dilution of the MeOH with H_2O, saturation with salt, and extraction with ether. The ether was washed with 5% $NaHCO_3$, dried, and removed under vacuum. Distillation gave **8** whose boiling point (70 °C at 1.5 Torr) compared favorably with that reported in the literature.[7] Methyl 2-pentynoate (**9**) was prepared from 2-pentynoic acid (Farchan Laboratories) as described for **8**. Its boiling point (83 °C at 0.1 Torr) also compared favorably with the literature value.[8] 1-Phenyl-2-propyn-1-one (**2**), 1-hexyn-3-one (**3**), and 4,4-dimethyl-1-pentyn-3-one (**5**) were obtained, as described below, by oxidation of their respective alcohols: 1-phenyl-2-propyn-1-ol (Aldrich), 1-hexyn-3-ol (Pfaltz and Bauer), and 4,4-dimethyl-1-pentyn-3-ol, prepared as described previously.[9] General oxidation procedure: 15.0 g (50.0 mmol) of sodium dichromate and 9.6 mL of concentrated H_2SO_4 were dissolved in 15 mL of H_2O. A 5.0 mL volume of each alcohol was added to 15 mL of glyme in a 50 mL flask with a condenser and heated to reflux. The dichromate solution was added to the alcohol/glyme mixture at the rate of 1 mL/min. After 2 h of reflux, water was added, and the product was extracted with CH_2Cl_2, washed with 5% $NaHCO_3$, and dried over $MgSO_4$. After removal of solvent under vacuum, **2** and **3** were distilled (bps: 60−70 °C/70 mm). Ketone **3** was confirmed by its bp;[10] **2** crystallized in the condenser and was confirmed by its mp.[10] The solvent from the isolation of **5** was removed by fractional distillation at atmospheric pressure. Ketone **5** was distilled at 120 °C which compared favorably with the literature.[9] Further purification of **5**, to remove glyme, was accomplished by preparative GC: 2.6 m × 1 cm glass column packed with DC550 on Chromosorb W at 75 °C and a He flowrate of 100 mL/min. Ketones **2**, **3**, and **5** were synthesized in high yield (>90%) and in 90−95% purity as determined by GC.

Chromatographic separations were performed with Prep Sep Extraction Columns obtained from Fisher Scientific.

Analysis Conditions. 300 MHz ^{1}H NMR, 60 MHz ^{1}H NMR, and 75.4 MHz ^{13}C NMR spectra are reported relative to Me_4Si in $CDCl_3$. Mass spectral analyses were obtained at 70 eV and are expressed as m/z and as relative intensity (%). Errors in exact masses do not exceed 3 ppm. GC and GC-MS analyses were done with a 25 m column of internal diameter 0.20 mm with a methyl silicone stationary phase of 0.33 μm film thickness.

Reductions with Tributyltin Hydride. Reduction of the dihalo acetals with tributyltin hydride was accomplished as follows: the solvent was removed from a reaction mixture and the product was dissolved in 400 μL of d_6-benzene in an NMR tube. The tube was placed in ice and 400 μL (1.5 mmol) of tributyltin hydride was added. After 1 h at room temperature, the solution was analyzed by NMR and/or GC-MS. When the latter procedure was used, the solution from the NMR tube was washed through a chromatography column before analysis by GC-MS.

Reaction Conditions for Terminal Alkynes. Ketones **1**, **2**, and **3** with NBS: the appropriate amount of concentrated

(8) Priebe, H. *Acta Scan. Ser. B* **1987**, *41*, 640.
(9) Barrelle, M.; Gilenat, R. *Bull. Soc. Chem.* **1967**, 453.
(10) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39.

H_2SO_4 (Table 1) was added with stirring to 1 mL of MeOH in an ice bath. The ice bath was removed as soon as the solution reached room temperature. To this solution were added 1 mmol of alkyne and 4 mmols of NBS. After 1.5 h, 3 mL of CCl_4 was added, and NBS and succinimide were filtered. The filtrate was washed with H_2O and saturated $NaHCO_3$, and the CCl_4 layer was separated, dried, and removed under vacuum. The crude product was added to 1 mL of THF and 1 mL of 9 M H_2SO_4 and stirred for 2 h to hydrolyze ketal-acetal to acetal and to remove a byproduct from the reaction of succinimide and acid (probably $MeO_2C(CH_2)_2CONH_2$, based on GC-MS) which interfered with chromatography. (Ketal-acetals are minor products except with **2** where the product composition is **11**, 21%, and **25**, 79%). The hydrolysis product was extracted with 3 mL of CCl_4, washed with a saturated $NaHCO_3$, and dried over $MgSO_4$. After solvent removal, dibromo acetals **10**−**12** were purified by chromatography with hexane/ether (1−2%).

Ketones **1**, **3**, and **4** with NIS: to 2 mmol of NIS in 0.5 mL of MeOH was added 0.5 mmol of alkyne. The appropriate amount of concentrated H_2SO_4 (Table 1) was dropped into this stirred solution. After 1 h, the reaction product was extracted with 1.5 mL of CCl_4, washed with saturated $NaHCO_3$, and dried over $MgSO_4$. The diiodo acetals **13**−**16** were not purified further because of decomposition. Ketone **2** with NIS: synthesis of **14** required a special approach since the reaction of **2** with NIS/MeOH/H_2SO_4 as described for **1**, **3**, and **4** led to a mixture of **14** and the diiodo acetal-ketal **26** (67% **14**, 33% **26**) which could not be hydrolyzed to **14**. Furthermore, **14** could not be separated cleanly from **26** by chromatography. Synthesis of **14**: to a stirred solution of 0.35 mL of MeOH and 0.15 mL of H_2O was added 450 mg of NIS and 65 mg of **2** and the appropriate amount of H_2SO_4. After 5 h, the reaction was worked up as described above to give **14** in high purity.

General Reaction Conditions for Internal Alkynes 6−9. All reactions were done by placing the appropriate amounts of alkyne and *N*-halosuccinimide in 0.6 mL of DMF/0.4 mL of H_2O/acid (concentrated H_2SO_4), if needed, in a small flask equipped with a magnetic stirrer. After appropriate reaction times, 2 mL of CCl_4 were added to the reaction mixtures. With NBS, the mixture was filtered. (Filtration was unnecessary with NIS). The organic layer was removed and washed with 5% $NaHCO_3$ and dried over $MgSO_4$.

Specific conditions that gave the best yields with NBS: **6** and **8**: 1 mmol of NBS, 0.334 mmol of alkyne, and react for 2 h. Then add a second mmol of NBS and react for another 2 h. **7** and **9**: 1 mmol of NBS, 0.25 mmol of alkyne, appropriate percent of H_2SO_4 (Table 2) by weight in DMF/H_2O, and react for 1 h. Specific conditions that gave the best yields with NIS: 1.55 mmol of NIS, 0.5 mmol alkyne, appropriate percent of H_2SO_4 (Table 2) by weight in DMF/H_2O, and react for 1 h.

Proof for the Structures of the Products from the Terminal Alkynes. 3,3-Dibromo-4,4-dimethoxybutan-2-one (10). The structure of **10** was confirmed (GC-MS) by reduction with tributyltin hydride to the known 4,4-dimethoxybutan-2-one (Aldrich) and by its high-resolution mass spectrum: HRMS (CI): MNH_4^+, calcd for $C_6H_{10}O_3Br_2NH_4$, 305.9340; found, 305.9348. ^{1}H NMR (300 MHz): δ 2.63 (s, 3H), 3.66 (s, 6H), 4.68 (s, 1H). ^{13}C NMR: δ 25.4, 59.0, 68.6, 106.6, 195.4. MS *m*/*z* (EI): 261, 259, 257 (*m*-OCH_3), 218, 216, 214 ($CH_3COCHBr_2$), 203 201, 199 (CBr_2CHO), 75 ($CH(OCH_3)_2$, 100), 43 (CH_3CO). IR (cm^{-1}): OCH_3, 2844; CO, 1731. GC analysis conditions: programmed from 55 to 220 °C at 10 °C/min; retention time (min), 11.2.

2,2-Dibromo-3,3-dimethoxy-1-phenylpropan-1-one (11). The structure of **11** was confirmed (GC-MS) by reduction with tributyltin hydride to the known[11] 3,3-dimethoxy-1-phenylpropan-1-one and by its high-resolution mass spectrum: HRMS (CI): MNH_4^+, calcd for $C_{11}H_2O_3Br_2NH_4$, 367.9497; found, 367.9484. ^{1}H NMR (300 MHz): δ 3.72 (s, 6H), 4.86 (s, 1H), 7.51−8.14 (m, 5H). ^{13}C NMR: δ 59.2, 65.3, 106.8, 127.9, 130.5, 133.2, 133.3, 188.9. MS *m*/*z* (EI): 218, 216, 214 (CBr_2CHO), 105 (C_6H_5CO, 100), 77 (C_6H_5), 75 ($CH(OCH_3)_2$). IR (cm^{-1}): OCH_3, 2850; CO, 1700. GC analysis conditions: programmed from 75 to 220 °C at 20 °C/min; retention time (min), 11.7.

2,2-Dibromo-1,1,3,3-tetramethoxy-1-phenylpropane (25). Acetal-ketal **25** was isolated from the reaction of alkyne **2** with NBS/MeOH/H_2SO_4 prior to hydrolysis to **11** by chromatography. ^{1}H NMR (60 MHz): δ 3.32 (s, 1H), 3.41 (s, 6H), 3.54 (s, 6H), 7.28−7.59 (m, 5H). GC/MS *m*/*z* (EI): 151 ($C_6H_5C(OCH_3)_2$, 100), 105 (C_6H_5CO), 75 ($CH(OCH_3)_2$). IR (cm^{-1}): OCH_3, 2846. GC analysis conditions: programmed from 75 to 220 °C at 20 °C/min; retention time (min), 14.3.

2,2-Dibromo-1,1-dimethoxyhexan-3-one (12). The structure of **12** was confirmed by its high-resolution mass spectrum: HRMS (CI): MNH_4^+, calcd for $C_8H_{14}O_3Br_2NH_4$, 333.9664; found, 333.9653. ^{1}H NMR (300 MHz): δ 0.96 (t, 3H, J = 7.2 Hz), 1.69 (sextet, 2H, J = 7.2 Hz), 3.00 (t, 2H, J = 7.2 Hz), 3.65 (s, 6H), 4.69 (s, 1H). ^{13}C NMR: 13.3, 17.9, 39.3, 59.0, 69.0, 106.6, 197.8. GC/MS *m*/*z* (EI): 289, 287, 285 (M − OCH_3), 218, 216, 214 ($CHBr_2COCH_3$), 203, 201, 199 (CBr_2CHO), 75 ($CH(OCH_3)_2$, 100), 43 (CH_3CO). IR (cm^{-1}): OCH_3, 2844; CO, 1728. GC analysis conditions: programmed from 55 to 220 °C at 20 °C/min; retention time (min), 8.7.

Reaction of Methyl Propiolate (4) with NBS/CH_3OH/H_2SO_4. Only a low yield (∼20% by GC) of dibromo acetal (methyl 2,2-dibromo-3,3-dimethoxypropanoate) was obtained in the reaction of **4** with NBS/CH_3OH/H_2SO_4. The product could not be isolated from the complex mixture by preparative GC or chromatography, but its structure was confirmed by GC-MS *m*/*z* (EI): 277, 275, 273 (M − OCH_3); 218, 216, 214 (*m* − OCH_3 − CO_2CH_3), 75 ($(CH_3O)_2CH$, 100), 59 (CO_2CH_3).

Reaction of 4,4-Dimethyl-1-pentyn-3-one (5). Compound **5** and NBS/CH_3OH/H_2SO_4 under all reaction conditions gave only a trace of desired acetal, 1,1-dimethoxy-2,2-dibromo-4,4-dimethylpentan-3-one, which was identified by its mass spectrum, GC-MS *m*/*z* (EI): 218, 216, 214 (CBr_2CHOCH_3), 85 ($(CH_3)_3CCO$), 75 ($CH(OCH_3)_2$, 100), 57 ($(CH_3)_3C$). The major products were the vinyl dibromo ketone, the tribromide (1,2,2-tribromo-4,4-dimethylpentan-3-one), and the tetrabromide (1,1,2,2,-tetrabromo-4,4-dimethylpentan-3-one); the structures of the tribromide and tetrabromide were confirmed by GC-MS, ^{1}H NMR, and ^{13}C NMR. NIS with **5** in CH_3OH/H_2SO_4 did not give the diiodo acetal but yielded a complex mixture whose components were not confirmed.

3,3-Diodo-4,4-dimethoxybutan-2-one (13). The structure of **13** was confirmed (GC-MS and ^{1}H NMR) by reduction with tributyltin hydride to the known 4,4-dimethoxybutan-2-one (Aldrich). ^{1}H NMR (300 MHz): δ 2.63 (s, 3H), 3.65 (s, 6H), 4.67 (s, 1H). ^{13}C NMR: δ 18.9, 25.5, 58.8, 107.5, 196.8. GC-MS *m*/*z* (EI): 384 (M^+), 353 (M − OCH_3), 310 (CI_2CHOCH_3), 75 ($CH(OCH_3)_2$, 100), 43 (CH_3CO). IR (cm^{-1}): OCH_3, 2842; CO, 1714. GC analysis conditions: programmed from 55 to 220 °C at 10 °C/min; retention time (min), 14.3.

2,2-Diiodo-3,3-dimethoxy-1-phenylpropan-1-one (14). The structure of **14** was confirmed (GC-MS and ^{1}H NMR) by reduction with tributyltin hydride to the known[10] 3,3-dimethoxy-1-phenyl-1-propane. ^{1}H NMR (300 MHz): δ 3.69 (s, 6H), 4.07 (s, 1H), 7.41−8.30 (m, 5H). ^{13}C NMR: δ 18.2, 59.0, 107.8, 128.4, 131.1, 132.7, 134.3, 182.7. IR (cm^{-1}): OCH_3, 2842; CO, 1740.

2,2-Diiodo-1,1,3,3-tetramethoxy-1-phenylpropane (26). Acetal-ketal **26** was separated from **14** by chromatography. ^{1}H NMR (300 MHz): δ 3.44 (s, 6H), 3.84 (s, 6H), 3.70 (s, 1H), 7.26−8.14 (m, 5H). ^{13}C NMR: δ 28.9, 51.2, 57.3, 104.2, 106.8, 127.9, 130.3, 132.5, 136.6. IR (cm^{-1}): 2842 (OCH_3).

2,2-Diiodo-1,1-dimethoxyhexan-3-one (15). The structure of 15 was confirmed by its high-resolution mass spectrum: HRMS (CI): MNH_4^+, calcd for $C_8H_{14}O_3I_2NH_4$, 429.9388; found 429.9376. ^{1}H NMR (300 MHz): δ 0.99 (t, 3H, J = 7.2 Hz), 1.70 (sextet, 2H, J = 7.2), 3.22 (t, 2H, J = 7.2), 3.67 (s, 6H), 3.95 (s, 1H). ^{13}C NMR: δ 13.3, 18.9, 19.1, 39.5, 58.9, 107.5, 199.0. GC-MS *m*/*z* (EI): 412, 381 (*m* − OCH_3), 310 (CI_2CHOCH_3), 75 ($CH(OCH_3)_2$, 100), 43 (CH_3CO). IR (cm^{-1}): OCH_3, 2842; CO, 1712. Purity (70%) was determined using benzene as an internal standard and integrating the methine

(11) DeKempe, N.; Verhe, R.; DeBuyck, L.; Tukiman, S.; Schamp, N. *Tetrahedron* **1979**, *35*, 789.

hydrogen. The impurities (30%) were suggested by ^{1}H NMR (integration of CH_3O groups) and could not be removed. GC analysis conditions: programmed for 45−200 °C at 10 °C/min; retention time (min), 16.3.

Methyl 2,2-Diiodo-3,3-dimethoxypropanoate (16). The structure of **16** was confirmed (GC-MS and ^{1}H NMR) by reduction with tributyltin hydride to the known methyl 3,3-dimethoxypropanoate (Aldrich). ^{1}H NMR (300 MHz): δ 3.69 (s, 6H), 3.86 (s, 3H), 3.93 (s, 1H). ^{13}C NMR: δ 0.4, 54.9, 59.5, 108.5, 167.7. GC-MS *m*/*z* (EI): 400 (M^+), 369 (M − OCH_3), 341 (M − CH_3CO_2), 294 (CI_2CHO), 242 (M − I, −OCH_3), 75 ($CH(OCH_3)_2$, 100), 59 (CH_3CO_2). IR (cm^{-1}): OCH_3, 2842; CO, 1739. GC analysis conditions: programmed for 45−200 °C at 10 °C/min; retention time (min), 16.3.

Proof for the Structures of the Products from the Internal Alkynes. 1-Phenyl-3,3-dibromo-1,3-butanedione (17). This compound was reported previously,[12] and its structure was established by comparison to the reported NMR spectrum. ^{1}H NMR (300 MHz): δ 2.51 (s, 3H), 7.35−8.15 (m, 5H). ^{13}C NMR: δ 24.7, 68.7, 128.6, 130.7, 130.8, 134.2, 185.2, 191.5. GC analysis conditions: programmed from 75 to 200 °C at 20 °C/min; retention time (min), 10.0.

3,3-Dibromo-2,4-hexanedione (18). The structure of **18** was confirmed (^{1}H NMR and GC-MS) by reduction with tributyltin hydride to the known 2,4-hexanedione.[13] ^{1}H NMR (300 MHz): δ 1.24 (t, 3H, J = 7.36), 2.62 (s, 3H), 3.00 (q, 2H, J = 7.36). ^{13}C NMR: 9.24, 24.5, 30.5, 68.1, 193.2, 196.9. GC-MS *m*/z (EI) 232, 230, 228 ($C_4H_6Br_2O$), 57 (C_2H_5CO, 100), 43 (CH_3CO). IR (cm^{-1}): CO, 1730. GC analysis conditions: programmed from 60 to 200 °C at 6 °C/min; retention time (min), 13.1.

Methyl 2,2-Dibromo-3-keto-3-phenylpropanoate (19). The structure of **19** was confirmed by its high-resolution mass spectrum: HRMS (CI): MNH_4^+, calcd for $C_{10}H_8Br_2O_3NH_4$, 351.9184; found, 351.9173. ^{1}H NMR (300 MHz): δ 3.84 (s, 3H), 7.46−8.02 (m, 5H). ^{13}C NMR: δ 55.1, 58.7, 128.6, 130.2, 130.4, 134.0, 165.1, 182.9. GC-MS *m*/*z* (EI): 258, 256 (M − Br), 202, 200, 198 ($COCBr_2$), 105 (C_6H_5CO, 100), 77 (C_6H_5). IR (cm^{-1}): CH_3O, 2847; CO, 1776 and 1722. GC analysis conditions: programmed from 75 to 200 °C at 20 °C/min; retention time (min), 12.2.

Methyl 2,2-Dibromo-3-ketopentanoate (20). The structure of **20** was confirmed (^{1}H NMR) by reduction with tributyltin hydride to the known methyl 3-ketopropanoate (Aldrich). Comparison of the compounds was made with ^{1}H NMR and GC-MS. ^{1}H NMR (300 MHz): δ 1.22 (t, 3H, J = 7.3 Hz), 2.96 (q, 2H, J = 7.3 Hz), 3.92 (s, 3H). ^{13}C NMR: 9.36, 29.5, 55.1, 59.0, 164.4, 194.7. GC-MS *m*/z (EI): 234, 232, 230 ($C_3H_4Br_2O_2$), 59 (CH_3OCO), 57 (C_2H_5CO, 100). GC analysis conditions: programmed from 45 to 200 °C at 10 °C/min; retention time (min), 12.2.

1-Phenyl-3,3-diiodo-1,3-butanedione (21). The structure of **21** was confirmed (^{1}H NMR) by reduction with tributyltin hydride to known 1-phenyl-1,3-butanedione (Aldrich) and by its high-resolution mass spectrum: HRMS (CI): MH^+, calcd for $C_{10}H_8I_2O_2H$, 414.8692; found, 414.8688. Comparison of the compounds was made by NMR and GC-MS. ^{1}H NMR (60 MHz): δ 2.60 (s, 3H), 7.40−8.03 (m, 5H). ^{13}C NMR: δ 22.3, 24.6, 128.7, 130.3, 130.9, 134.0, 186.5, 193.5. IR (cm^{-1}): CO, 1700. Diiodide **9** is a solid and was recrystallized from hexane: mp 56−57 °C.

3,3-Diiodo-2,4-hexanedione (22). The structure of **22** was confirmed (^{1}H NMR and GC-MS) by reduction with tributyltin hydride to the known 2,4-hexanedione.[13] ^{1}H NMR (300 MHz): δ 1.23 (t, 3H, J = 7.2 Hz), 2.81 (s, 3H), 3.17 (q, 2H, J = 7.2 Hz). ^{13}C NMR: δ 10.6, 22.7, 23.3, 29.6, 195.1, 198.5. GC-MS *m*/z (EI): 366 (m^+), 323 ($C_2H_5COCI_2$), 309, (CH_3COCI_2), 57 (C_2H_5CO), 43 (CH_3CO, 100). IR (cm^{-1}): CO, 1713. GC analysis conditions: programmed from 60 to 200 °C at 10°/min; retention time (min), 15.3.

Methyl 2,2-Diiodo-3-keto-3-phenylpropanoate (23). The structure of **23** was confirmed by its high-resolution mass spectrum: HRMS (CI): MNH_4^+, calcd for $C_{10}H_8O_3I_2NH_4$, 447.8910; found, 447.8907. ^{1}H NMR (300 MHz): δ 3.77 (s, 3H), 7.40−8.02 (m, 5H). ^{13}C NMR: δ 2.15, 55.3, 128.1, 128.6, 130.4, 133.6, 167.3, 184.6. IR (cm^{-1}): CH_3O, 2842; CO, 1747 and 1684. Diiodide **11** is a solid and was recrystallized from hexane: mp 74−76 °C.

Methyl 2,2-Diiodo-3-ketopentanoate (24). The structure of **24** was confirmed (^{1}H NMR) by reduction with tributyltin hydride to the known methyl 3-ketopropanoate (Aldrich) and by its high-resolution mass spectrum: HRMS (CI): MNH_4^+, calcd for $C_{10}H_8O_3I_2NH_4$, 447.8910; found, 447.8907. ^{1}H NMR (300 MHz): δ 1.25 (t, 3H, J = 7.2 Hz), 3.07 (q, 2H, J = 7.2 Hz), 3.98 (s, 3H). ^{13}C NMR: δ 3.70, 10.6, 27.6, 55.2, 166.5, 195.9. GC-MS *m*/*z* (EI): 382 (M^+), 326 ($CH_3OCOCHI_2$), 294 ($COCI_2$), 59 (CH_3CO), 57 (C_2H_5CO, 100). IR (cm^{-1}): CH_3O, 2842; CO, 1739. GC analysis conditions: programmed from 45 to 200 °C at 10 °C/min; retention time (min), 15.1.

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Supporting Information Available: NMR spectra of new compounds (33 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(12) Yoshida, J.; Yano, S.; Ozawa, T.; Kawabata, N. *J. Org. Chem.* **1985**, *50*, 3470.

(13) Hampton, K. R.; Harris, T. M.; Hauser, C. R. *J. Org. Chem.* **1965**, *30*, 61.