Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Ling-Guo Meng [a], Pei-Jie Cai [a], Qing-Xiang Guo [a] & Song Xue [a]
[a] Department of Chemistry, University of Science and Technology of China, Hefei, China
Published online: 18 Jan 2008.

To cite this article: Ling-Guo Meng, Pei-Jie Cai, Qing-Xiang Guo & Song Xue (2008) Direct Iodination of Monosubstituted Aryl Acetylenes and Acetylenic Ketones, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 38:2, 225-231, DOI: 10.1080/00397910701749724

To link to this article: http://dx.doi.org/10.1080/00397910701749724

Synthetic Communications®, 38: 225–231, 2008

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910701749724

Direct Iodination of Monosubstituted Aryl Acetylenes and Acetylenic Ketones

Ling-Guo Meng, Pei-Jie Cai, Qing-Xiang Guo, and Song Xue

Department of Chemistry, University of Science and Technology of China, Hefei, China

Abstract: Monosubstituted acetylenes were iodinated to form iodoacetylenes under simple conditions. Reaction of aryl acetylenes with molecular iodine in the presence of 4-dimethylaminopyridine (DMAP) gave the desired products in good to excellent yields. Iodination of aryl acetylenic ketones using K_2CO_3 as base was also described.

Keywords: acetylenic ketones, bases, iodination, terminal alkynes

Iodoacetylenes are useful intermediates in organic synthesis,[1] and medicinal and pharmaceutical research.[2] Numerous synthetic methods for their preparation have been developed.[3] The usual preparative methods include iodination of metal aceylides RC≡CM (M=Li,[1c,4] Na,[5] or Mg[6]) performed from terminal acetylenes. The direct iodination of terminal alkynes using ZnI_2,[3d] silver nitrate,[1b,3f] morphine,[1a,2a,3g] liquid ammonia,[7] and tetrabutylammonium trifluoroacetate[8] have also been reported. Herein, we describe an alternative methodology to synthesize iodoacetylenes by direct iodination of monosubstituted acetylenes using molecular iodine and a base.

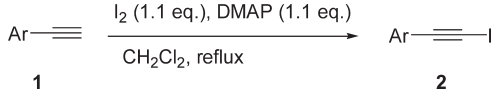
Received March 22, 2007
Address correspondence to Song Xue, Department of Chemistry, University of Science and Technology of China, 96 JinZhai Rd., Hefei 230026, China. E-mail: xuesong@ustc.edu.cn

RESULTS AND DISCUSSION

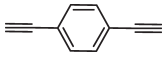
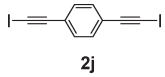
To begin our study, phenylacetylene was chosen as a representative substrate for reaction conditions. Treatment of phenylacetylene with 1.1 equiv of 4-dimethylaminopyridine (DMAP) and 1.1 equiv of molecular iodine in CH_2Cl_2 under reflux for 6 h afforded (2-iodoethynyl)benzene (**2a**) in 90% yield. When the reaction was stirred at room temperature, 88% yield of the desired product was obtained by prolonging reaction time to 24 h. When 1.1 equiv of 1,4-diazabicyclo[2,2,2]octane (DABCO) was used as a base, the desired product **2a** was obtained in a low yield (64%) under the same conditions. However, the choice of pyridine and Et_3N as base gave a mixture of (2-iodoethynyl)benzene (**2a**) and (1,2-diiodovinyl)benzene in combined 63% and 24% yields, respectively. Thus, DMAP as a base was crucial for the course of this reaction. The use of toluene and diethyl ether as solvent led to the formation of the desired product **2a** in 32% and 22% yields, respectively.

Subsequently, various terminal acetylenes were submitted to the reaction, and the results are shown in Table 1. Aryl acetylenes could be converted to the corresponding 1-iodo-1-alkynes effectively, and the substrate with an electron-withdrawing group on the aromatic ring gave better yield than that of an electron-donating group on the aromatic ring. Treatment of

Table 1. Iodination of terminal acetylenes using DMAP



1 **2**

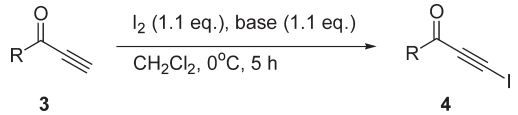
Entry	Ar	Time (h)	Product	Yield[a] (%)
1	C_6H_5	6	**2a**	90
2	*p*-ClC_6H_4	6	**2b**	95
3	*o*-ClC_6H_4	10	**2c**	85
4	*p*-BrC_6H_4	10	**2d**	93
5	*o*-BrC_6H_4	10	**2e**	88
6	*p*-$NO_2C_6H_4$	10	**2f**	97
7	*m*-$NO_2C_6H_4$	10	**2g**	96
8	*p*-EtC_6H_4	10	**2h**	87
9	*p*-$MeOC_6H_4$	12	**2i**	83
10		12	 **2j**	92[b]

[a]Isolated yields.
[b]DMAP (2.2 eq.) and iodine (2.2 eq.) were used.

1,4-diethynylbenzene with 2.2 equiv of DMAP and 2.2 equiv of iodine in CH_2Cl_2 under reflux for 12 h afforded the desired product **2j** in 92% yield. The reactions reported in Table 1 were clean, taking place with only trace amounts of 1,2-diiodoalkenes. The iodination of alkyl acetylene, however, was very slow under the similar conditions. For example, treatment of 1-octyne with DMAP and molecular iodine in CH_2Cl_2 at reflux for 12 h afforded a mixture of 1-iodooct-1-yne and 1,2-diiodooct-1-ene, which were not separated by silica-gel column chromatography. ^{1}H NMR spectra of the crude mixture indicated that only 37% of start materials was converted to 1-iodooct-1-yne and 1,2-diiodooct-1-ene with a ratio of 4:1. The iodination of alkyl acetylenes with diminished efficiency might be ascribed to the lower reactivity of alkyl acetylenes than that of aryl acetylenes.

Based on this work, we further study the iodination of terminal acetylenic ketones, which should be more reactive than aryl acetylenes. When 1-phenyl-prop-2-yn-1-one **3a** was submitted to the reaction under the standard conditions, no iodoacetylene was obtained. Fortunately, iodination of acetylenic ketones proceeded smoothly when inorganic base K_2CO_3 was used instead of DMAP. Reaction of substrate **3a** with 1.1 equiv of K_2CO_3 and 1.1 equiv of molecular iodine in CH_2Cl_2 under reflux for 5 h afforded the

Table 2. Iodination of acetylene ketones with iodine and bases



3 **4**

Entry	R	Base	Product	Yield[a] (%)
1	C_6H_5	K_2CO_3	**4a**	71[b]
2	C_6H_5	K_2CO_3	**4a**	82
3	C_6H_5	K_2CO_3	**4a**	70[c]
4	C_6H_5	$KHCO_3$	**4a**	<5
5	C_6H_5	KOH	**4a**	23
6	C_6H_5	Na_2CO_3	**4a**	13
7	*p*-ClC_6H_4	K_2CO_3	**4b**	83
8	*o*-ClC_6H_4	K_2CO_3	**4c**	84
9	*p*-FC_6H_4	K_2CO_3	**4d**	80
10	*p*-$MeOC_6H_4$	K_2CO_3	**4e**	88
11	*trans*-$C_6H_5CH{=}CH$	K_2CO_3	**4f**	89
12	OC_2H_5	K_2CO_3	**4g**	55

[a]Isolated yields.
[b]At reflux.
[c]At -10°C.

3-iodo-1-phenylprop-2-yn-1-one **4a** in 71% yield (entry 1, Table 1). The yield of the desired product was improved to 82% at 0°C. When other inorganic bases, such as $KHCO_3$, KOH, and Na_2CO_3, were used, much lower yields were obtained. Hence, K_2CO_3 was used to react with acetylenic ketones and molecular iodine for 5 h in CH_2Cl_2 at 0°C as the standard conditions. Subsequently, various acetylenic ketones were submitted to the reaction under the standard conditions, and representative results are shown in Table 2. As we described previously, aryl acetylenic ketones could be converted to the corresponding products. The substituents on the aromatic ring have no obvious effect on the reaction. The substrate containing electron-poor olefin underwent a selective iodination reaction in preference to addition of the olefin under our standard reaction conditions (entry 11, Table 2). Ethyl propiolate was also converted to the desired product, albeit the yield was moderate (entry 12, Table 2). However, 3-butyn-2-one as substrate gave an unidentified complex mixture. To date, there have been no reports of the iodination of acetylenic ketones. Therefore, a simple and efficient procedure involving mild conditions was provided to iodinate the aromatic acetylenic ketones.

In summary, we have developed an efficient method for the preparation of iodoacetylenes. The iodination reaction of aryl acetylenes with molecular iodine proceeded smoothly in the presence of DMAP, giving the desired products in good to excellent yields. The aryl acetylenic ketones were iodinated by molecular iodine and K_2CO_3 in good yields under mild conditions.

EXPERIMENTAL

Infrared (IR) spectra were run on a Bruker AC spectrometer and expressed in centimeters^{-1}. NMR spectra were recorded on a Bruker AVMCE-300 MHz in CD_3Cl solutions. High-resolution mass spectra were obtained with a Micromass GCT TOF mass spectrometer.

General Procedure for the Direct Iodination of Monosubstituted Aryl Acetylenes (Representative Procedure for Compound 2a)

Phenylacetylene (0.5 mmol) was added to a solution of DMAP (0.55 mmol) and iodine (0.55 mmol) in dry CH_2Cl_2 (2 mL) in a round flask. The resulting mixture was refluxed for the required length of time. The contents were cooled at room temperature, washed with sodium thiosulfate to remove unreacted iodine, and extracted with diethyl ether (3 × 10 mL). Subsequently, the extract was washed with brine (10 mL), dried over $MgSO_4$, and concentrated. The crude product was purified by silica-gel chromatography, and the corresponding product was isolated (102.6 mg, 90% yield).

General Procedure for the Direct Iodination of Monosubstituted Acetylenic Ketones (Representative Procedure for Compound 4a)

1-Phenylprop-2-yn-1-one (0.5 mmol) was added at 0°C to a solution of K_2CO_3 (0.55 mmol) and iodine (0.55 mmol) in dry CH_2Cl_2 (2 mL) in a round flask. The resulting mixture was stirred for 5 h. The contents were washed with sodium thiosulfate to remove unreacted iodine and extracted with diethyl ether (3 × 10 mL). Then, the extract was washed with brine (10 mL), dried over $MgSO_4$, and concentrated. The crude product was purified by silica-gel chromatography, and the corresponding product was isolated (105 mg, 82% yield).

Data for New Compounds

3-Iodo-1-phenylprop-2-yn-1-one (4a): ^{1}H NMR (300 MHz, $CDCl_3$) δ, ppm, 8.15 (d, $J = 7.6$ Hz, 2H), 7.65 (t, $J = 7.3$ Hz, 1H), 7.52 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ, ppm, 176.5, 136.3, 134.6, 129.9, 128.8, 94.1, 20.0; IR (KBr) ν, cm^{-1}, 2148, 1613; HRMS (EI) calcd. for C_9H_5OI (M^+): 255.9385; found: 255.9380.

1-(4-Chlorophenyl)-3-iodoprop-2-yn-1-one (4b): ^{1}H NMR (300 MHz, $CDCl_3$) δ, ppm, 8.07 (d, $J = 8.5$ Hz, 2H), 7.48, (d, $J = 8.5$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ, ppm, 175.2, 141.3, 134.7, 131.2, 129.2, 93.8, 21.0; IR (KBr) ν, cm^{-1}, 2150, 1630; HRMS (EI) calcd. for C_9H_4OClI (M^+): 289.8995; found: 289.9001.

1-(2-Chlorophenyl)-3-iodoprop-2-yn-1-one (4c): ^{1}H NMR (300 MHz, $CDCl_3$) δ, ppm, 8.07 (d, $J = 8.1$ Hz, 1H), 7.48 (m, 2H), 7.41 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ, ppm, 175.0, 134.9, 133.9, 133.8, 133.2, 131.8, 126.9, 95.0, 21.8; IR (KBr) ν, cm^{-1}, 2145, 1633; HRMS (EI) calcd. for C_9H_4OClI (M^+): 289.8995; found: 289.8992.

1-(4-Fluorophenyl)-3-iodoprop-2-yn-1-one (4d): ^{1}H NMR (300 MHz, $CDCl_3$) δ, ppm, 8.18 (m, 2H), 7.19 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ, ppm, 174.9, 166.8, 132.8, 132.7, 116.1, 93.9, 20.3; IR (KBr) ν, cm^{-1}, 2149, 1629; HRMS (EI) calcd. for C_9H_4OFI (M^+): 273.9291; found: 273.9294.

3-Iodo-1-(4-methoxyphenyl)prop-2-yn-1-one (4e): ^{1}H NMR (300 MHz, $CDCl_3$) δ, ppm, 8.11 (d, $J = 8.7$ Hz, 2H), 6.97 (d, $J = 8.7$ Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ, ppm, 175.1, 164.8, 132.3, 129.6, 114.1, 94.1, 55.7, 19.1; IR (KBr) ν, cm^{-1}, 2150, 1623; HRMS (EI) calcd. for $C_{10}H_7O_2I$ (M^+): 285.9491; found: 285.9488.

(*E*)-5-Iodo-1-phenylpent-1-en-4-yn-3-one (4f): ^{1}H NMR (300 MHz, $CDCl_3$) δ, ppm, 7.84 (d, $J = 16.2$ Hz, 1H), 7.65 (m, 2H), 7.43 (m, 3H), 6.79

(d, $J = 16.2$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ, ppm, 176.6, 149.5, 133.9, 131.5, 129.1, 128.8, 127.9, 93.7, 18.7. IR (KBr) v, cm^{-1}, 2147, 1644; HRMS (EI) calcd. for $C_{11}H_7OI$ (M^+) 281.9542; found: 281.9538.

ACKNOWLEDGMENTS

We express our appreciation to the National Natural Science Foundation of China (20776114) and Program of NCET (060551).

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