

One-pot synthesis of monosubstituted aryl(hetaryl)acetylenes by direct introduction of the C≡CH residue into arenes and hetarenes

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Abstract—A convenient one-pot synthesis of aryl(hetaryl)acetylenes by cross-coupling of aryl(hetaryl)iodides with acetylene in presence of PdCl₂(Ph₃)₂, CuI and K₂CO₃ in DMF has been developed.

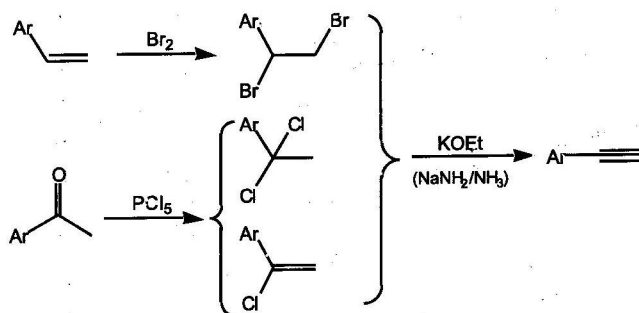
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1. Introduction

The diverse and high reactivity of the C≡C bond and the unusually high CH-acidity of monosubstituted acetylenes has determined an unabated interest on 1-alkynes for many years.^{1–4} The C≡CH moiety is susceptible of nucleophilic, electrophilic, radical and cycloaddition reactions, and can be used both for functionalizing and building up C–C bonds. In fact, terminal acetylenes are very important key-compounds in the widely applied Mannich,⁵ Hay,⁶ Cadiot-Chodkiewicz,⁷ and Sonogashira-Heck⁸ reactions for preparing the corresponding propargyl-amines, symmetrical and unsymmetrical 1,3-diynes and disubstituted acetylenes.

Ethynyl derivatives occupy a special place, because monosubstituted acetylenes have not only a reactive triple bond but also an active hydrogen which allows to carry out various transformations of the molecule with preservation of the multiple bond. The properties of such compounds as C–H acids are used for functionalization and construction of C–C bonds.

Usually classical methods for preparing aryl(hetaryl)alk-1-ynes involve the sequence halogenation–dehalogenation of vinyl aromatic compounds⁹ or halogenation–dehydrohalogenation of dihaloderivatives from vinylarenes(hetaryenes) or methylaryl(hetaryl)-ketones (Scheme 1).¹⁰



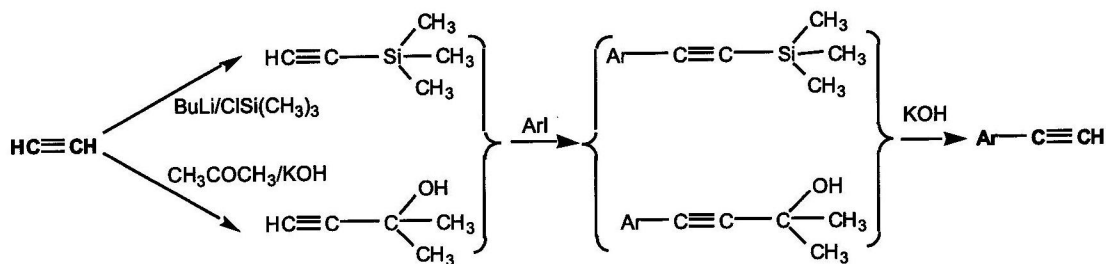
Scheme 1.

However, a review of the publications dealing with the study of the transformations of vinylic or ketonic groups into acetylenes under the action of bases indicates the sensitivity of these reactions to experimental conditions, the structure of the starting substrate and the nature of the base.^{10,11} Thus, the yields of all possible isomers of ethynylpyridine and ethynylquinoline obtained by the dehydrohalogenation varied from 0.1 to 33%.¹⁰ An attempt to dehydrobrominate a pyrrolo-dibromoderivative under the action of sodium ethoxide failed.¹⁰ The present authors¹² found that pyrazolylvinylchlorides, which are not substituted at the nitrogen of the ring, under the effect of sodium amide lead to complex mixtures.

In the last three decades, beginning from the discovery of Japanese chemists who found new effective catalysts for the cross-coupling reaction of arylhalides with monosubstituted acetylenes,¹⁰ this method has become the main one for producing not only disubstituted, but also monosubstituted arylacetylenes. This approach involves protecting one end

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Scheme 2.

of acetylene, introduction of 1-alkyne via coupling at the free end of acetylene, followed by deprotection of the acetylenic moiety of aryl- or heteroarylacetylenes (Scheme 2).

A usual way for ethynylarene synthesis involves the cleavage of the tertiary acetylenic alcohols or trimethylsilylacetylene derivatives by treatment with a catalytic amount of alkali. However, the starting reagent, trimethylsilylacetylene, is rather expensive and gives only trimethylsilyl derivatives. On the other hand, the second method—base-induced cleavage of α -acetylenic alcohols into carbonyl and ethynyl compounds (the reverse Favorsky reaction) requires hard reaction conditions (strong alkali, high temperature) and cannot be applied for obtaining labile acetylenic compounds.

In 1980 Japanese chemists tried to carry out cross-coupling of aryl iodides with acetylene itself using the typical catalytic system $\text{PdCl}_2(\text{PPh}_3)_2\text{-CuI-R}_3\text{N}$ for preparing of ethynylarenes (Scheme 3). But their attempts were unsuccessful; the main products being tolanes as a result of the reaction of the arylalk-1-yne formed with the starting iodo component.^{1,13}

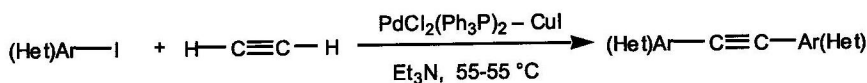
We supposed that this negative result was related with using volatile amines, having high vapor pressure, which decrease partial pressure of acetylene and therefore its concentration. Nevertheless, we undertook a first attempt to carry out the cross-coupling of acetylene with iodoarenes and -hetarenes for preparing the desired monosubstituted acetylenes.¹⁴ For

achieving our aim we changed the traditional conditions of a reaction of cross-coupling. In this paper we describe full experimental conditions and new additional examples.

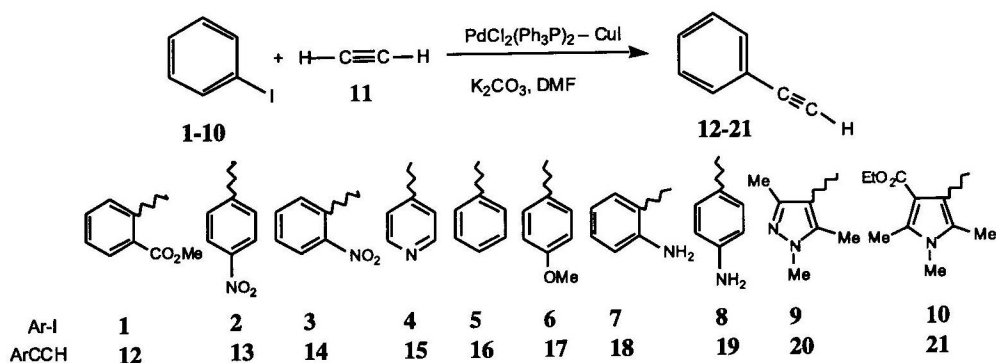
We have proposed that it is necessary to have a large excess of acetylenes in the reaction mixture for diminishing the competition reaction of the iodoarene with the initially generated ethynylarene. Thus, we decided to use a solvent with high boiling point and which dissolves large amounts of acetylene. Dimethylformamide is a solvent, which has just such properties. Below is given the solubility of $\text{HC}\equiv\text{CH}$ at 20 °C and 760 mm Hg in different solvents: volumes of $\text{HC}\equiv\text{CH}$ per 1 volume of solvent: ether 5.5, THF 18.5, DMF 33–37.¹⁵ To increase additionally the high concentration of $\text{HC}\equiv\text{CH}$ we used a relatively large amount of DMF (the weight ratio iodide/DMF=1:200).

It is also known that the application of stronger bases in cross-coupling substantially increases the reaction rate, thus we used potassium carbonate instead of the usual di- and trialkylamines. Taking into account the facts mentioned above, we carried out cross-coupling of a series of iodoarenes and -hetarenes in an acetylene current in the presence of catalytic amounts of $\text{PdCl}_2(\text{PPh}_3)_2$, CuI and excess of K_2CO_3 in DMF at 50–55 °C (Scheme 4).

Iodoarenes and hetarenes with low reactivity like *p*-iodoaniline, 4-iodo-1,3,5-trimethylpyrazole, 4-iodo-3-ethoxycarbonyl-1,2,5-trimethylpyrrole, due to the strong +M-effect of the nitrogen atom underwent ethynylation in low yields



Scheme 3.



Scheme 4.

Table 1. Ethynylarenes and -hetarenes

Compound	Time, h	Yield, % (% from copper salt)	Boiling points (melting points), °C	Literature
<i>o</i> -Ethynylcarbomethoxybenzene (12)	12	73.2 (56.4)	80–85/1 Torr $n_d^{22}=1.5550$	14
<i>p</i> -Ethynylnitrobenzene (13)	12.5	76.4	146.5–147.5	19
<i>o</i> -Ethynylnitrobenzene (14)	8	64.4	79.5–81	19
4-Ethynylpyridine (15)	17	60.2	96–97	21
Phenylacetylene (16)	17	60.0 (56.4)	44/23 Torr $n_d^{17}=1.5507$	19
<i>p</i> -Ethynylanisole (17)	17	64.2 (50.0)	27–28 96–98/14 Torr	19
<i>p</i> -Ethynylaniline (18)		(10.0)	99–100	19
<i>o</i> -Ethynylaniline (19)		(47.4)	99–101/13 Torr	19
4-Ethynyl-1,3,5-trimethyl-1 <i>H</i> -pyrazole (20)	36	24.0 (20.3)	45.5–56.5	11
4-Ethynyl-1,2,5-trimethyl-3-carbomethoxy-1 <i>H</i> -pyrrole (21)		35.4 (20.0)	87.5–88.5	22

(15–35%). Iodobenzene and even *p*-methoxyiodobenzene gave monoarylated products in moderate yields (50–55%). Iodoarenes (hetarenes) with electron withdrawing substituents gave the desired ethynyl derivatives in high yields (65–75%).

The different behavior of *p*- and *o*-iodoaniline is noteworthy. The yield in the case of the deactivated *o*-iodoaniline was rather high (50%). We explain this fact by the proximity of the amino group in *ortho*-position to the halogeno atom, which assist the formation of the complex of palladium salt followed by the introduction of palladium between carbon and iodine atoms—the first step of the cross-coupling. We had already observed the same trends for other analogous cases.¹⁶

Our studies on the one-pot synthesis of aryl(hetaryl)alk-1-ynes from iodoarenes(hetarenes) show that target compounds can be prepared in moderate yields (60–75%) for activated iodides and in low yields (15–35%) from halo derivatives with low reactivity. Unusual results were obtained for *o*- and *p*-iodoanilines. For the experimental details of the synthesis as well as physical constants and yields of ethynyl derivatives see Section 2 and Table 1.

2. Experimental

2.1. General procedures

Melting points were determined with a hot-stage microscope. Column chromatography was performed on silica gel (Merck 60, 70–230 mesh). The R_f values were measured on aluminium backed TLC plates of silica gel 60 F254 (Merck, 0.2 mm) with the indicated eluent. ¹H NMR spectra were recorded on a Bruker DRX 400 (9.4 T, 400.13 MHz) spectrometer. Chemical shifts (δ in ppm) are given from internal CHCl₃ (7.24 ppm). Coupling constants (J in Hz) are accurate to ± 0.2 Hz. Mass spectra (HRMS) were measured at 70 eV using the electron impact mode. Commercially available iodoarenes **2–8** ('Aldrich') were used without additional purification. Iodides **1**,¹⁷ **9**,¹⁸ **10**¹⁹ were prepared by previously reported methods. Copper(I) acetylides were prepared from liquid acetylenes (**12**, **17–21**) according to the published procedure.²⁰

2.2. General procedures of ethynylation

The flask was fitted with a gas inlet tube, thermometer and dropping funnel. After a rubber stopper fitted with a glass

tube was tightly placed on the flask, the air was replaced by acetylene (purified from acetone passing through water and then sulfuric acid). The flask was charged with 260 mL of DMF, powdered potassium carbonate (2 g, 15 mmol), PdCl₂(Ph₃P)₂ (50 mg) and CuI (25 mg). After the mixture was additionally saturated with acetylene with vigorous stirring, the temperature was raised up to 50 °C and a solution of iodides **1–10** (10 mmol) in 30–40 mL of DMF (also previously saturated with acetylene) was slowly added during 5–6 h. Reaction was carried out at 50–55 °C and under a permanent stream of acetylene up to completion of the reaction (TLC control).

After cooling the reaction mixture to room temperature, 700 mL of ether (or 700 mL of chloroform) and then 800–900 mL of water was added. The aqueous layer was extracted twice with ether [or CHCl₃ (2×100 mL)]. The combined organic solutions were washed three times with 200 mL of water in order to remove as much as possible of the DMF and were dried over MgSO₄. After filtering the solution through a thick layer of neutral Al₂O₃ (3×2 cm) on a sintered-glass funnel, the solvent was removed to dryness under reduced pressure. The desired acetylenes were purified by distillation or by recrystallization. Time of reaction, yields and melting point of compounds are reported in Table 1.

Acknowledgements

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References and notes

- Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627.
- Ames, D. E.; Bull, D.; Takundwa, C. *Synthesis* **1981**, 364.
- Austin, W. B.; Bilow, N.; Kelleghan, W. J.; Lau, K. S. Y. *J. Org. Chem.* **1981**, *46*, 2280.
- Brandsma, L.; Vasilevsky, S. F.; Verkruijse, H. D. *Application of Transition Metal Catalysts in Organic Synthesis*; Springer: Berlin, 1998.
- Helmann, H.; Opitz, G. *α -Aminoalkylierung*; Chemie: Weinheim, 1960.
- Hay, A. S. *J. Org. Chem.* **1962**, *27*, 3320.
- Cadiot, P.; Chodkiewicz, W., *Chemistry of Acetylenes*; Viehe, H.G.; (Ed.) Marcel Dekker, New York, 1969, p 597.

8. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *50*, 4467.
9. Brandsma, L. *Preparative Acetylenic Chemistry*; Springer: Amsterdam, 1971.
10. Vasilevsky, S. F.; Tretyakov, E. V.; Elguero, J. *Adv. Heterocycl. Chem.* **2001**, *82*, 1.
11. Shvartsberg, M. S.; Vasilevskii, S. F.; Kostrovskii, V. G.; Kotlyarevsky, I. L. *Khim. Geterotsikl. Soedin.* **1969**, *6*, 1055.
12. Shvartsberg, M. S.; Vasilevskii, S. F.; Sagdeev, R. Z.; Kotlyarevsky, I. L. *Izv. Akad. Nauk SSSR, Ser. Khim* **1969**, *6*, 927.
13. Sakamoto, T.; Kondo, Y.; Yamanaka, M. *Heterocycles* **1988**, *27*, 2225.
14. Author's Certificate No. 943234, **1982**, USSR (Vasilevsky, S.F.; Shvartsberg, M.S.; Kotlyarevsky, I.L.). Published in: *Otkrytiya i izobreteniya*, **1982**, *26*, 117.
15. Chodkiewicz, W. *Ann. Chim.* **1957**, *13*, 819.
16. Vasilevsky, S. F., Doct. Thesis, Novosibirsk, USSR, **1986**.
17. Shvartsberg, M. S.; Moroz, A. A. *Izv. Akad. Nauk SSSR, Ser. Khim* **1971**, *7*, 1582.
18. Knorr, L. *Chemische Berichte* **1895**, *28*, 714.
19. Allen, A. D.; Cook, C. D. *Can. J. Chem.* **1963**, *41*, 1084.
20. Stephens, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 3313.
21. Shvartsberg, M. S.; Kozhevnikova, A. N.; Kotlyarevsky, I. L. *Izv. Akad. Nauk SSSR, Ser. Khim* **1971**, *8*, 1833.
22. Vasilevskii, S. F.; Sundukova, T. A.; Shvartsberg, M. S.; Kotlyarevsky, I. L. *Izv. Akad. Nauk SSSR, Ser. Khim* **1980**, *8*, 1871.