An improved procedure for the synthesis of substituted acetylenes from the reaction of acetylene gas with aryl iodides under palladium–copper catalysis [1]

Manojit Pal and Nitya G. Kundu *

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Calcutta – 700 032, India

Dimethylformamide facilitated the palladium–copper catalysed reaction of acetylene gas with aryl iodides in a closed system to give disubstituted acetylenes in fair to excellent yields. Use of chloroform as solvent gave mixtures of mono- and di-substituted acetylenes.

Whilst substituted acetylenic compounds are of interest because of their occurrence in nature,[2–4] many diaryl acetylenes of the structure *p*-$AC_6H_4C{\equiv}CC_6H_4D$-*p* (D and A are electron donor and acceptor groups, respectively) have been synthesized and investigated recently for their spectroscopic and electronic properties.[5]

Diarylacetylenes have also been synthesized for the purpose of intramolecular recognition[6] whilst such compounds have potential as intermediates in synthesis.[7,8]

A number of methods[9] have been used to prepare substituted acetylenes including the coupling of aryl halides with copper(I) acetylides, the Castro reaction,[10] and the palladium-catalysed coupling of aryl halides with terminal alkynes[11–17] to give disubstituted compounds. The drawback to these methods is, however, that mono-substituted acetylenes are needed as starting materials. Brandsma and co-workers[18] have synthesized mono-substituted acetylenes by the palladium-catalysed reaction of vinylic, aromatic or heteroaromatic bromides and trimethylsilyl acetylene whilst Cassar[11] synthesized mono- and di-substituted acetylenes from acetylene gas. Hagihara and co-workers[19] reported a palladium-catalysed synthesis of symmetrical diaryl- and heteroaryl-acetylenes from acetylene gas and aryl halides under a nitrogen atmosphere. This method has only been used for aryl or heteroaryl halides soluble in diethylamine and has not been further studied.

During work on the palladium-catalysed reactions of acetylenic substrates to obtain compounds of biological significance,[20–24] we needed a variety of aryl and hetero-aryl substituted acetylenes. In applying Hagihara's procedure to our work however, we experienced rapid loss of solvent and poor product yields. When we used dimethylformamide (DMF) as a solvent in a closed system, *e.g.*, a balloon full of acetylene gas attached to the reaction flask, however, the product yields improved considerably. This constitutes an improved and efficient method for the synthesis of substituted acetylenes in which aryl or heteroaryl halides, **1–8**, are heated under an oxygen-free atmosphere of acetylene (held in a balloon) in the presence of bis(triphenylphosphine)palladium chloride, copper(I) iodide and Et_3N in DMF (Scheme 1 and Table 1).

$$\underset{\textbf{1–8}}{ArX} + HC{\equiv}CH \xrightarrow[\substack{Et_3N,\ Cu^{I}I\\ \text{in DMF}}]{[Pd(PPh_3)_2]Cl_2} \underset{\textbf{10–21}}{ArC{\equiv}CAr} \qquad (1)$$

Results and discussion

Both aromatic and heterocyclic iodides could be used for this reaction (see Table 1), the former (entries 1, 3 and 4) giving better product yields than the latter (entries 5 and 9). Bromides gave poor product yields (entries 2, 6 and 7). Various substituents (*e.g.* Cl, CHO and MeO) were well-tolerated in this reaction, with electron-withdrawing groups improving the product yields considerably (entry 3 *vs.* 1 and entry 8 *vs.* 5).

Although the palladium-catalysed reactions usually took place readily either at room temperature (30 °C) or at 60 °C for 12 h, in certain cases (with less reactive iodides) a longer period (48 h) was needed to optimize the yield. Triethylamine was the best base and reactions were carried out in closed systems in order to prevent both reagent and solvent evaporation. The use of 5 equiv. of triethylamine was critical, since with only 2 equiv. the product yields were lower, *e.g.* 34% (entry 13) *vs.* 59% (entry 10). The use of $NaHCO_3$ (5 equiv.) as base, entry 10, also led to a lower product yield (41%). The reaction was also moisture sensitive, no product being isolated in the presence of 5% water (entry 9).

Catalysts

Although it was found that the product yield was lowered (21%, entry 11) in presence of CuI but absence of $[Pd(PPh_3)_2]Cl_2$, in the absence of CuI but presence of $[Pd(PPh_3)_2]Cl_2$ it was zero (entry 12). This indicates that CuI is an essential co-catalyst in the reaction. The use of $Pd^{II}OAc$ in place of $[Pd(PPh_3)_2Cl_2]$ also led to lower product yields.

Solvents

Since the use of diethylamine, the original solvent,[19] failed to give the desired products, we chose instead dimethylformamide, most of the pyrimidines and uracils in which we were interested being soluble in it. Generally only disubstituted, no mono-substituted, acetylenes were obtained (entries 1, 3–5, 8–10). Use of chloroform, a less polar solvent, gave a mixture of di- and mono-substituted acetylenes (entries 15–17). Curiously, reactions in chloroform gave highest product yields when acetylene was passed through the reaction mixture. Mono-substituted acetylene yields increased with the less reactive iodides (entry 17 *vs.* 15 or 16). This may be explained in terms of the lower reactivity of **19** compared to **17** and **18**.

Unsymmetrically disubstituted acetylenes

In the preparation of unsymmetrically disubstituted acetylenes an equimolar mixture of aryl iodides was treated with acetylene gas in dimethylformamide in a closed system at room temperature (35 °C) for 48 h to give two symmetrically disubstituted and an unsymmetrically disubstituted acetylene, the latter being the major product.

Aromatic halides ArX (**1**–**8**)			Products ArC≡CAr (or H) (**10**–**21**)	
	Ar	X	X	X′
1	Ph	I	Ph	Ph
2	Ph	Br	*m*-ClC_6H_4	*m*-ClC_6H_4
3	*m*-ClC_6H_4	I	1-naphthyl	1-naphthyl
4	1-naphthyl	I	2-thienyl	2-thienyl
5	2-thienyl	I	5-CHO-2-thienyl	5-CHO-2-thienyl
6	2-thienyl	Br	Pyrim	Pyrim
7	5-CHO-2-thienyl	Br	Urac	Urac
8	Pyrim	I	Ph	H
9	5-Iodo-1,2,3,4-tetrahydropyrimidine-2,4-dione		*m*-ClC_6H_4	H
			Pyrim	H
			Pyrim	Ph
			Pyrim	*m*-ClC_6H_4

Pyrim = 2,4-dimethoxypyrimidin-5-yl
Urac = 2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl

Scheme 1

Table 1 Palladium–copper catalysed reaction of aromatic halides (ArX) with acetylene gas

		Reaction conditions[a]		
Entry	Aromatic halide	Solvent, *T*/°C, *t*/h	Products	Yields[b] (%)
1	**1**	DMF, 60, 12	**10**	83
2	**2**	DMF, 60, 12	**10**	12
3[c]	**3**	DMF, 30, 12	**11**	97
4	**4**	DMF, 30, 12	**12**	92
5	**5**	DMF, 30, 12	**13**	66
6	**6**	DMF, 30, 12	No product	
7	**6**	DMF, 60, 12	**13**	17
8	**7**	DMF, 60, 12	**14**	96
9	**8**	DMF, 30, 48	**15**	63
10	**8**	DMF, 60, 12	**15**	59
11[d]	**8**	DMF, 60, 12	**15**	21
12[e]	**8**	DMF, 60, 12	No product	
13[f]	**8**	DMF, 60, 12	**15**	34
14	**9**	DMF, 60, 12	**16**	14
15	**1**	$CHCl_3$, 30, 6	**10** + **17**	61 (2:1)
16	**2**	$CHCl_3$, 30, 6	**11** + **18**	59 (2:1)
17	**8**	$CHCl_3$, 30, 6	**15** + **19**	61 (1:1)
18	**1** + **8** (1:1)	DMF, 35, 48	**10** + **20** + **15**	70 (1:2:1)
19	**3** + **8** (1:1)	DMF, 35, 48	**11** + **21** + **15**	74 (1:2:1)

[a] Reactions in entries 1–14 and 18–19 were carried out in a closed system in an atmosphere of acetylene gas held in a 2 dm^3 balloon; the reactions in entries 15–17 were carried out with a slow stream of acetylene gas being passed through the reaction mixture. [b] Refers to the overall yield. [c] In the case of entry 3, when a combination of $Pd(OAc)_2$ and CuI was used in place of $[Pd(PPh_3)_2]Cl_2$ and CuI, the yield was 67% rather than 97%. [d] CuI (catalytic) was used only, instead of $[Pd(PPh_3)_2]Cl_2$ and CuI as in entry 10. [e] Only $[Pd(PPh_3)_2]Cl_2$ (catalytic) was used instead of $[Pd(PPh_3)_2]Cl_2$ and CuI. [f] 2 Equiv. of triethylamine used as base.

Conclusions

In the described procedure, closed-system reactions were conveniently carried out in dimethylformamide as a solvent under an atmosphere of acetylene gas to give exclusively disubstituted acetylenes mostly in modest to excellent yields. Of these, compound **13** was converted into the naturally occurring 5-[(2-thienyl)ethynyl]thiophene-2-carbaldehyde.[25] Also, since direct coupling of **9** with acetylene gave **16** only in poor yield, the latter was obtained (51%) by demethylation of compound **15** with 6 mol dm^{-3} hydrochloric acid; compound **16** is of potential biological interest.

Use of chloroform as a solvent gave mixtures from which the monosubstituted acetylenes could be easily separated, some of which have potential biological interest. Thus, 5-ethynyl-2,4-dimethoxypyrimidine **19** was demethylated (Me_3SiCl, NaI, MeCN; or 6 mol dm^{-3} hydrochloric acid) to give 5-ethynyluracil.[26,27]

Experimental

Mps were determined on a Reichert (285980) (Austria) bath. UV spectra were recorded on a Hitachi 200-20 spectrometer in spectrophotometric grade ethanol (Baker). IR spectra were taken on a Perkin-Elmer 298 instrument as KBr plate or liquid films. ^1H NMR spectra were recorded on a Varian XL-200 spectrometer, a Varian EM-360 spectrometer, Bruker AC 300 and Bruker 200 spectrometers in solvents as indicated with tetramethylsilane as internal reference; *J* values given in Hz. Mass spectra were recorded on a Kratos-profile spectrometer. Silica gel TLC was performed on 60F-254 pre-coated sheets (E. Merck) and column chromatography was done on silica gel (60–120 mesh). Elemental analyses were performed on a Perkin-Elmer 240C analyser. The aryl halides were synthesized according to the known procedures.[28–31]

General procedure for the synthesis of symmetrical 1,2-disubstituted acetylenes

To a solution of aromatic or heteroaromatic halide (2 mmol) in dimethylformamide (5 cm^3) were added bis(triphenylphosphine)palladium(II) chloride (0.07 mmol), cuprous iodide (0.23 mmol) and triethylamine (10 mmol). The mixture was stirred in the presence of an excess of oxygen-free acetylene (in a balloon) according to the conditions (time and temperature) indicated in Table 1. At the end of the reaction period, the solvent was removed under high vacuum and the residue was purified by column chromatography on silica gel using light-petroleum (bp 60–80 °C) and chloroform as eluents. Compound **16** was purified by washing with light-petroleum (bp 60–80 °C),

followed by chloroform and then crystallization from aqueous methanol.

Unsymmetrical diaryl substituted acetylenes **20** and **21** (entries 18 and 19, respectively) were synthesized in reactions carried out with a mixture of the aryl or heteroaryl halides (1 : 1 molar ratio) dissolved in dimethylformamide; other conditions were as described above. The reactions in entries 15–17, were carried out with passage of a slow stream of acetylene gas through the reaction mixture (500 mg of iodide in 50 cm^3 of chloroform).

1,2-Diphenylacetylene 10. Mp 57–59 °C (lit.,[32] 59–61 °C).

1,2-Di(*m*-chlorophenyl)acetylene 11. Mp 81–82 °C; ν_{max}(KBr)/cm^{-1} 1595s, 1560m, 1480s and 1420m; λ_{max}(EtOH)/nm 302 (log ε 4.28), 295 (4.29), 283 (4.45) and 267 (4.31); δ_H(60 MHz, $CDCl_3$) 7.33 (6 H, m, ArH) and 7.50 (2 H, m, ArH) (Found: C, 68.3; H, 3.5. $C_{14}H_8Cl_2$ requires C, 68.01; H, 3.23%).

1,2-Di(1-naphthyl)acetylene 12. Mp 126–127 °C; ν_{max}(KBr)/cm^{-1} 1585s, 1500s, 1405s and 1300m; λ_{max}(EtOH)/nm 356.6 (log ε 4.27), 340.6 (4.34) and 334.6 (4.33); δ_H(60 MHz, $CDCl_3$) 7.3–7.86 (12 H, m, ArH) (Found: C, 94.65; H, 5.4. $C_{22}H_{14}$ requires C, 94.96; H, 5.03%).

1,2-Di(2-thienyl)acetylene 13. Mp 93–95 °C; ν_{max}(KBr)/cm^{-1} 1530w, 1430s, 1410s and 1200s; λ_{max}(EtOH)/nm 330.8 (log ε 4.09), 322.6 (4.15), 315 (4.22), 304.2 (4.17) and 255.8 (4.03); δ_H(60 MHz, $CDCl_3$) 6.92–7.06 (2 H, m, ArH) and 7.23–7.26 (4 H, m, ArH) (Found: C, 62.75; H, 3.18. $C_{10}H_6S_2$ requires C, 63.15; H, 3.15%).

1,2-Di(5-formyl-2-thienyl)acetylene 14. Mp 158–159 °C; ν_{max}(KBr)/cm^{-1} 1655s, 1460s, 1380s, 1330b and 1215s; λ_{max}(EtOH)/nm 384.2 (log ε 4.43), 361.8 (4.52) and 281 (4.02); δ_H(60 MHz, $CDCl_3$) 7.46 (2 H, d, *J* 8, ArH), 7.76 (2 H, d, *J* 8, ArH) and 10.33 (2 H, s, CHO) (Found: C, 58.3; H, 2.5. $C_{12}H_6O_2S_2$ requires C, 58.53; H, 2.43).

1,2-Bis(2,4-dimethoxypyrimidin-5-yl)acetylene 15. Mp 193–194 °C; ν_{max}(KBr)/cm^{-1} 1610s, 1655s, 1470s, 1410s and 1390s; λ_{max}(DMF)/nm 349.8 (log ε 3.48), 328.8 (4.18), 308.8 (4.33), 298 (4.24) and 256 (4.13); *m*/*z* 303 (M^+, 100%) (Found: C, 55.45; H, 4.7; N, 18.7. $C_{14}H_{14}N_4O_4$ requires C, 55.63; H, 4.63; N, 18.54%).

1,2-Di(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)acetylene 16. Mp >230 °C; ν_{max}(KBr)/cm^{-1} 1700s, 1660s and 1640s; δ_H(300 MHz, [$^2H_6$]-DMSO) 8.03 (2 H, s, pyrimidinyl 6-H) and 11.65 (4 H, s, NH) (Found: C, 48.7; H, 2.7; N, 22.5. $C_{10}H_6N_4O_4$ requires C, 48.78; H, 2.44; N, 22.76%).

Phenylacetylene 17. Bp 139–141 °C (lit.,[33] bp 142–144 °C); δ_H(60 MHz, CCl_4) 3.00 (1 H, s, HC≡C) and 7.15–7.7 (5 H, m, ArH).

***m*-Chlorophenylacetylene 18.** Oil; ν_{max}(neat)/cm^{-1} 3270s and 2105w; λ_{max}(EtOH)/nm 256 (log ε 4.4) and 249 (4.38); δ_H 3.00 (1 H, s, HC≡C) and 7.14–7.4 (4 H, m, ArH) (Found: C, 70.0; H, 3.45. C_8H_5Cl requires C, 70.07; H, 3.65%).

2,4-Dimethoxypyrimidin-5-ylacetylene 19. Mp 70–72 °C (lit.,[26] 78–80 °C); δ_H(60 MHz, $CDCl_3$) 3.33 (1 H, s, C≡CH), 4.03 (3 H, s, OCH_3), 4.06 (3 H, s, OCH_3) and 8.33 (1 H, s, 6-H).

1-(2,4-Dimethoxypyrimidin-5-yl)-2-phenylacetylene 20. Mp 49–51 °C; ν_{max}(KBr)/cm^{-1} 1600s, 1590s and 1550s; λ_{max}(EtOH)/nm 282 (log ε 4.27) and 297 (4.26); δ_H(60 MHz, $CDCl_3$) 3.8 (3 H, s, OCH_3), 4.0 (3 H, s, OCH_3) and 7.34 (5 H, m, ArH) (Found: C, 69.8; H, 4.9; N, 11.9. $C_{14}H_{12}N_2O_2$ requires C, 70.0; H, 5.0; N, 11.66%).

1-(*m*-Chlorophenyl)-2-[2,4-dimethoxypyrimidin-5-yl]acetylene 21. Mp 96–98 °C; ν_{max}(KBr)/cm^{-1} 1600s, 1585s and 1550s; λ_{max}(EtOH)/nm 282 (log ε 4.38) and 299.4 (4.41) (Found: C, 60.75; H, 4.1; N, 10.3. $C_{14}H_{11}ClN_2O_2$ requires C, 61.09; H, 4.00; N, 10.18%).

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