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One-Step Synthesis of Aromatic Terminal Alkynes from Their Corresponding Ketones under Microwave Irradiation

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Abstract: One-step microwave-assisted synthesis of phenylacetylenes **2a–j** from the corresponding ketones **1a–j** in the presence of a new reagent, PCl_5–pyridine, is described. The reaction is carried out under a simple operational and experimental procedure, avoiding the use of the complicated and harsh multistep reaction.

Keywords: Microwave activation, One-step synthesis, PCl_5–pyridine reagent, Phenylacetylene derivatives

INTRODUCTION

Acetylenic groups are important targets for organic chemists because of their applications and rich chemistry.[1] Conventional synthetic methods suggested in the literature for preparing these compounds[2] require multistep procedures with complicated preparation conditions, demanding vigilance during the whole reaction.[3] Although these methods are suitable for many synthetic routes, most of them have drawbacks such as applying sensitive chemicals (e.g., butyl lithium) and very low temperature (ca. $-78^{\circ}C$) under an inert atmosphere.[4] Recently, novel procedures have been developed in which

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the use of a proper co-catalyst under phase-transfer catalysis conditions,[5] a supported reagent[6] and a prepared in situ reagent have been reported.[7]

Besides, multistep preparations and multiple isolation processes cause low yields and high labor time. Thus, a direct synthesis of these compounds by a one-step reaction of a common substrate with a new and efficient reagent remains a great challenge for organic chemists.

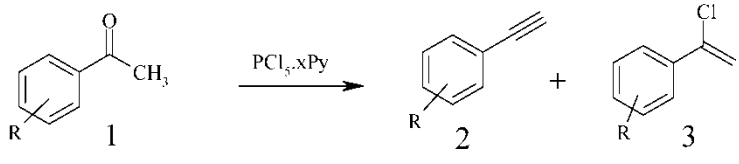
RESULTS AND DISCUSSION

During the past few years, the one-pot syntheses of interesting target molecules that require multistep procedures have gained increasing attention. In this context, the use of the microwave irradiation method is one of the most promising approaches.[8] On the other hand, the unique property of phosphorus reagents facilitates diverse organic reactions.[9] One of the most common methods is the conversion of α-dihalo carbonyls to the corresponding acetylenics in the presence of a strong base. Although this method is an economical process because of its cheap starting materials (ketones), it suffers from some drawbacks such as long labor time, a multistep procedure, and low yields.

In the development of new methods for functional group transformations in our laboratory, we were especially interested in improving the scope of the reaction. Considering the recent progresses in rapid synthesis methodologies such as the microwave method,[10] we were keen to carry out the conversion of the mentioned ketones to their corresponding acetylenics in a one-step reaction. Use of a new reagent based on phosphorus and the microwave irradiation technique (as a rapid process) allowed us to obtain 40 to 82% yields in a short period of time.

Our recent work on phosphorus based reagents (using $PCl_3 \cdot 3Py$ for converting hydroxyl-containing carboxylic acids to arylanilides)[11] prompted us to investigate on the appetite of PCl_5 and pyridine adduct for reactions that consisted of preparing acetylenic compounds from ketones. In continuation of our earlier activities on using microwave methods in organic synthesis[12] and significant effects of this method on the rate of reactions, we were interested to apply it for preparing acetylenic compounds (Scheme 1).

PCl_5/KOH[13] or $PCl_5/NaNH_2$[14] are known reagents in the two-step reaction of ketones. We tried the use of PCl_5/KOH or $PCl_5/NaNH_2$ in a one-step reaction; nevertheless, it led to an unusable reagent. This observation



Scheme 1.

Table 1. Optimization of time of the reaction for preparing **2d** under microwave irradiation

Pyridine/ PCl_5 (mol ratio)	Time (s)	Yield (%)
5	60	40
5	90	42
5	120	42
5	150	44
5	180	48
5	210	50
5	240	50

made us study the effects of PCl_5/pyridine in this reaction. This stable reagent is relatively mild to convert ketones to acetylenics under microwave irradiation. Initially, we carried out the same reaction under classical experimental conditions using a refluxing utility for 2.5 h which resulted in a very low yield (from 5 to 15%). In contrast, the reaction progressed easier under microwave irradiation to confirm the nonthermal effects of microwave irradiation in this reaction.[10]

As shown in Tables 1 and 2, the best reaction time found for preparing **2d** is at 210 s, and the best molar ratio of PCl_5 to pyridine for this product is (1 : 9). The strong affinity of phosphorus for oxygen atoms caused the initial bond between oxygen of the carbonyl group and phosphorus. At these conditions, α-hydrogen atoms become more acidic and are abstracted readily by a weak base such as pyridine, and eventually acetylenic compound is produced.

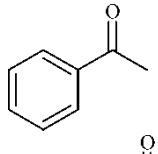
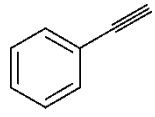
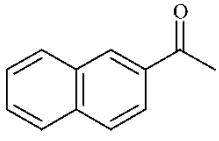
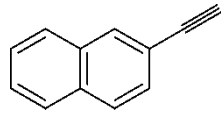
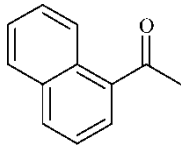
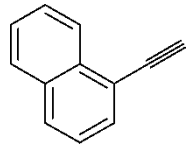
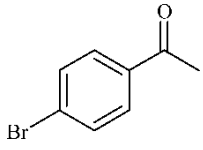
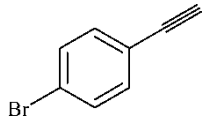
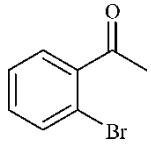
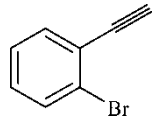
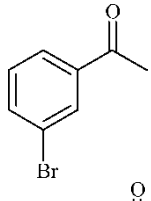
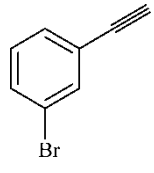
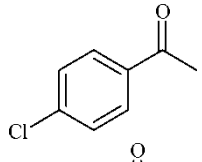
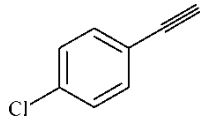
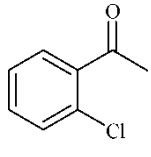
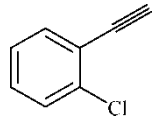
The optimizations made in Tables 1 and 2 are for all acetylenic compounds reported in this paper except for **2i** and **j**. For these products the reaction time was optimized to 60 s, and the best ratio found for the molar ratio of PCl_5 to pyridine was 1 : 18 instead of 1 : 9.

The crude reaction mixtures were directly analyzed by GC-MS and/or subjected to column chromatography. The reaction conditions and yields of

Table 2. Optimization of the molar ratio of pyridine to PCl_5 for preparing **2d** under microwave irradiation

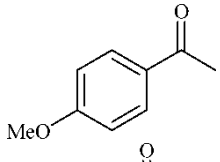
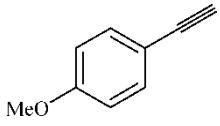
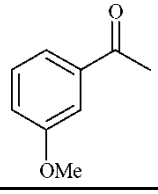
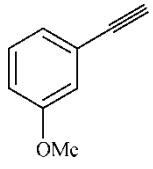
Pyridine/ PCl_5 (mol ratio)	Time (s)	Yield (%)
6	210	52
7	210	60
8	210	72
9	210	82
10	210	80

Table 3. Synthesis of phenylacetylene derivatives using ($PCl_5 \cdot Py$) reagent under microwave activation

Entry	Substrate 1	Product 2	Irradiation time (s)	Yield[a] (%)	3[d,b] (%)
a			210	74[b] (61)[c]	3
b			210	58 (50)	36
c			210	59 (52)	39
d			210	88 (82)	12
e			210	90 (82)	10
f			210	67 (54)	33
g			210	87 (77)	13
h			210	77 (72)	2

(*continued*)

Table 3. Continued

Entry	Substrate 1	Product 2	Irradiation time (s)	Yield[a] (%)	3[d,b] (%)
i			60	57 (40)	29
j			60	69 (51)	9

[a]All products were characterized by GC-MS and ^{1}H NMR.
[b]GC yield.
[c]Isolated yield.
[d]By-product **3**: α-chlorostyrene derivative.

the products (i.e., phenylacetylene derivatives **2**) are given in Table 3. These results indicate that **2a**–**j** were directly synthesized in a one-step reaction from **1a**–**j** using $PCl_5 \cdot 9Py$ as reagent.

Our observation showed that the presence of electron-donating groups on the aromatic nuclei enhanced the rate of reaction. The presence of oxygen-bearing functional groups such as methoxy group on the aromatic ring, because of its complexation with phosphorus and its conversion to a

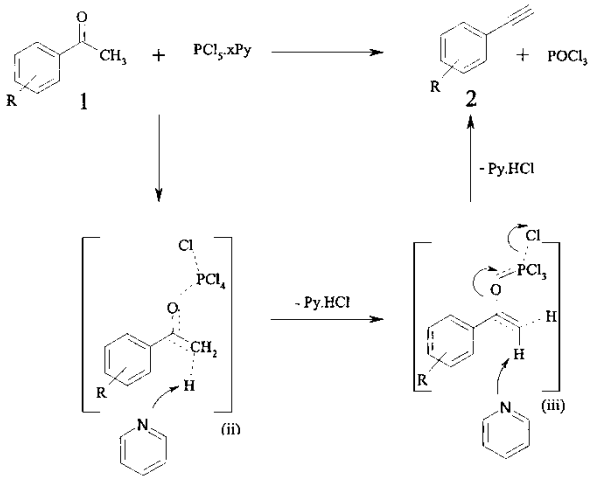


Figure 1.

negative induction group, diminished the yield. With respect to this observation the following mechanism was proposed for this reaction.

Our studies showed that a few α-chlorostyrene (**3**) was produced. To overcome this issue, the time of irradiation and the ratio of the reagent to ketone were tested, and increasing the ratio of pyridine to PCl_5 was more effective. The excess of pyridine trapped the liberated HCl and caused the abstraction of hydrogen from α-position to be easier. It is important to note that when pyridine had a low ratio (PCl_5·5Py), the excess of liberated HCl produced an additional amount of α-chlorostyrene (**3**) because of the absence of an effective base.

CONCLUSION

In summary, we have introduced a novel reagent for the one-step conversion of aromatic terminal alkynes from their corresponding ketones (entirely available chemicals) within a few minutes under microwave activation.

EXPERIMENTAL

Ketones, pyridine, and PCl_5 are commercially available.

^{1}H NMR (80 MHz) spectra were recorded on a Bruker 80-MHz spectrometer in $CDCl_3$ using TMS as internal standard. A GC-MS method for the analysis of mixtures was applied. A Fisons instruments gas chromatograph 8000 connected to a mass detector (Trio 1000) with 70 eV was used. A 30 m × 0.25 mm column packed with Wall Coated Open Tabular (WCOT) fused silica CP-sil 5CB-MS (from CHROMPAC in which MS shows the high quality of capillary column for the designed GC-MS and has a low bleeding) was employed. Column temperature was programmed from 80 to 270°C at 10°C/min. Injection was performed at 280°C. The carrier gas was helium, and the inlet pressure was 10 psi. A modified domestic microwave oven, equipped with a refluxing utility and a temperature controller, from Panasonic (model NN-C781JF operating at 2450 MHz) was used for all syntheses carried out in a monomode cavity.

General Experimental Procedure

Preparation of Reagent

(*CAUTION: PCl_5 is very corrosive and pyridine is highly toxic)*. In a 100-ml beaker, 9 mmol (0.725 ml) [18 mmol (1.45 ml) for **1i–j**] of dry and freshly distilled pyridine were placed. While stirring, 1 mmol (0.208 g) of phosphorus pentachloride was added gradually to make $PCl_5 \cdot Py$ reagent.

General Procedure

It is essential to work under a powerful hood to minimize the inhalation of chemicals.

*Synthesis of **2a, 2d–h***

A mixture of ketone **1a, 1d–h** (1 mmol), and $PCl_5 \cdot Py$ reagent (1 mmol) was refluxed at 110°C in a 50-ml flask for 210 s in microwave oven. After cooling in air, the mixture was washed with HCl (2%) to remove the pyridine and then extracted by dichloromethane (3×20 ml). The organic layer was separated and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated and the crude product was analyzed by GC-MS. The residue was purified from the by-product (α–chlorostyrene derivatives) and starting ketone (if existing) by fractional distillation apparatus. The identification of the isolated products was generally performed by ^{1}H NMR and MS spectral analyses.

*Synthesis of **2b–c***

A mixture of ketone **1b** and **c** (1 mmol) and $PCl_5 \cdot Py$ reagent (1 mmol) was refluxed at 110°C in a 50-ml flask for 210 s in microwave oven. After cooling in air, the crude product was analysed by GC-MS. Silica gel (1 g, 100 mesh) was added to the mixture, which became a free-flowing powder. The powder was separated, and the residue was purified by flash chromatography on dry silica gel (5 g, 100 mesh) using a short column (eluent: light petroleum ether).

*Synthesis of **2i** and **j***

A mixture of ketone **1i** and **j** (1 mmol) and PCl_5·Py reagent (0.5 mmol) was refluxed at 110°C in a 50-ml flask for 60 s in microwave oven. After cooling in air, the crude product was analysed by GC-MS. Silica gel (1 g, 100 mesh) was added to the mixture, which became a free-flowing powder. The powder was separated, and the residue was purified by flash chromatography on dry silica gel (5 g, 100 mesh) using a short column (eluent: light petroleum ether).

Phenylacetylene (Table 3, entry 2a): Oil.[15a] ^{1}H-NMR (80 MHz, $CDCl_3$): $\delta = 7–8$ (m, 5H), 3.20 (s, 1H). MS (EI, 70 eV): m/z (%) = 103 ($M^+ + 1$, 9), 102 (M^+, 100), 76 (20), 51 (7), 50 (8).

(2-Naphythyl)acetylene (Table 3, entry 2b): Oil.[15a] ^{1}H-NMR (80 MHz, $CDCl_3$):$\delta = 7–8.5$ (m, 7H), 3.29 (s, 1H). MS (EI, 70 eV): m/z (%) = 152 (M^+, 100), 98 (30), 78 (62), 64 (40), 53 (30).

(1-Naphthyl)acetylene (Table 3, entry 2c): Oil.[15a] ^{1}H-NMR (80 MHz, $CDCl_3$): $\delta = 7-8.5$ (m, 7H), 3.29 (s, 1H). MS (EI, 70 eV): m/z (%) = 153 ($M^+ + 1$, 28), 152 (M^+, 100), 98 (20), 76 (60), 63 (40), 50 (30).

(4-Bromophenyl)acetylene (Table 3, entry 2d): mp 64°C.[15a,d] ^{1}H-NMR (80 MHz, $CDCl_3$): $\delta = 7.2-7.5$ (AA′ BB′, 4H, $J_{AB} = 5.47$ Hz) 3.05 (s, 1H). MS (EI, 70 eV): m/z (%) = 182 ($M^+ + 2$, 97), 180 (M^+, 100), 101 (89), 75 (78), 50 (30).

(2-Bromophenyl)acetylene (Table 3, entry 2e): Oil.[15a,d] ^{1}H-NMR (80 MHz, $CDCl_3$): $\delta = 7.6$ (d, 1H), 7.5 (d, 1H), 7.2 (t, 1H), 7.1 (t, 1H), 3.3 (s, 1H). MS (EI, 70 eV): m/z (%) = 182 ($M^+ + 2$, 98), 180 (M^+, 100), 101 (55), 75 (70), 50 (35), 37 (15).

(3-Bromophenyl)acetylene (Table 3, entry 2f): Oil.[15a,d] ^{1}H-NMR (80 MHz, $CDCl_3$): $\delta = 7.7$ (s, 1H), 7.5 (d, 1H), 7.4 (d, 1H), 7.2 (t, 1H), 3.29 (s, 1H). MS (EI, 70 eV): m/z (%) = 182 ($M^+ + 2$, 98), 180 (M^+, 100), 101 (73), 75 (60), 50 (80).

(4-Chlorophenyl)acetylene (Table 3, entry 2g): mp 45°C.[15b,c,d] ^{1}H-NMR (80 MHz, $CDCl_3$): $\delta = 7.3-7.6$ (AA′BB′, 4H, $J_{AB} = 6.27$ Hz) 3.05 (s, 1H). MS (EI, 70 eV): m/z (%) = 138 ($M^+ + 2$, 30), 136 (M^+, 100), 101 (30), 74 (60), 50 (65).

(2-Chlorophenyl)acetylene (Table 3, entry 2h): Oil.[15b,c,d] ^{1}H-NMR (80 MHz, $CDCl_3$): $\delta = 7.5$ (d, 1H), 7.4 (d, 1H), 7.3 (t, 1H), 7.2 (t, 1H), 3.30 (s, 1H). MS (EI, 70 eV): m/z (%) = 138 ($M^+ + 2$, 25), 136 (M^+, 100), 101 (68), 74 (99), 50 (98).

(4-Methoxyphenyl)acetylene (Table 3, entry 2i): Oil.[15e] ^{1}H-NMR (80 MHz, $CDCl_3$): $\delta = 6.8.-7.6$ (AA′BB′, 4H, $J_{AB} = 9.99$ Hz) 3.79 (s, 3H), 3.30 (s, 1H). MS (EI, 70 eV): m/z (%) = 132 (M^+, 90), 117 (48), 89 (100), 63 (75), 62 (48), 39 (26).

(3-Methoxyphenyl)acetylene (Table 3, entry 2j): Oil.[15e] ^{1}H-NMR (80 MHz, $CDCl_3$): $\delta = 6.5-7.4$ (m, 4H) 3.79 (s, 3H), 3.20 (s, 1H). MS (EI, 70 eV): m/z (%) = 132 (M^+, 100), 102 (80), 89 (65), 63 (40), 62 (38), 39 (33).

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