Triphenylphosphine-Catalyzed Reaction of Aldehydes and Acetylenic Ketones with 1,3-Dicarbonyl Moieties: Synthesis of Multi-Carbonyl Compounds

Song Xue,* Qing-Fa Zhou, Le-Zheng Li, Qing-Xiang Guo

Department of Chemistry, University of Science and Technology of China, Hefei 230026, P. R. of China
Fax +86(551)3606689; E-mail: xuesong@ustc.edu.cn

Received 7 August 2005

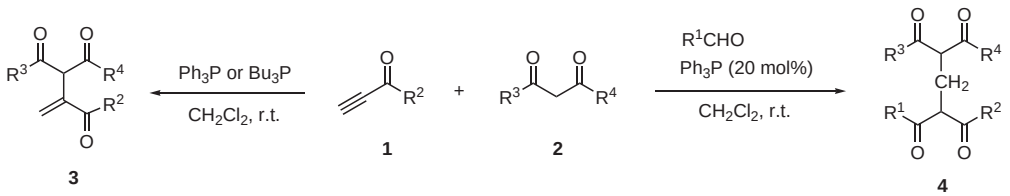
Abstract: A mild and efficient domino process of aldehydes, acetylenic ketones and 1,3-dicarbonyl moieties catalyzed by triphenylphosphine is reported. The method supplies a facile way to synthesize multi-carbonyl compounds in moderate to good yields. A plausible mechanism is proposed for this domino reaction.

Key words: acetylenic ketones, PPh_3, carbon–carbon bond formation, multi-carbonyl compounds

The formation of carbon–carbon single bonds is of fundamental importance in organic synthesis.[1] Increasing demand for 'green chemistry' urges development of new carbon–carbon bond forming reaction with defined chemo- and stereoselectivity and high atom economy.[2] Among the well-documented synthetic methods, domino reactions constitute a very attractive approach to the rapid formation of complex architecture in one simple, safe, environmentally acceptable and resource-effective operation.[3] However, relatively few domino strategies have been directed toward the production of acyclic structural motifs despite significant advances in the area of acyclic stereocontrol.[4]

Phosphines are useful mild reagents in various organic reactions,[5,6] such as isomerization,[7] β-addition,[8] γ-addition,[9] and [3+2] cycloaddition.[10] Recently, α-addition of activated methylenes to alkynoates catalyzed by phosphine to provide multifunctional compounds have been reported.[11] The olefins bearing 1,3-dicarbonyl moieties **3** could be synthesized by α-addition of 1,3-dicarbonyl compounds to electron-deficient alkynes in the presence of phosphine under mild conditions (Scheme 1). Herein we wish to report a mild and efficient domino process of aldehydes, acetylenic ketones and 1,3-dicarbonyl moieties catalyzed by triphenylphosphine for preparing acyclic multi-carbonyl compounds **4** (Scheme 1). To our best knowledge, the triphenylphosphine-catalyzed multi-component reaction is rather limited so far.

Our initial studies began with an investigation of the domino process of benzaldehyde, phenyl acetylenic ketone and 2,4-pentanedione under various conditions. When benzaldehyde (0.3 mmol), 1-phenylprop-2-yn-1-one (0.36 mmol) and 2,4-pentanedione (0.36 mmol) were dissolved in 3 mL CH_2Cl_2 at 0 °C, PPh_3 (20 mol%) was added, then the mixture was warmed to room temperature and stirred for six hours.[12] We found that the product **4a** could be isolated in 41% yield along with 22% yield of **3a**, which was formed by α-addition of 2,4-pentanedione to 1-phenylprop-2-yn-1-one. Compounds **3a** and **4a** were firmly identified by ^1H NMR and ^{13}C NMR and MS spectra. Other solvents such as THF, toluene, MeCN were usable, and the reactions in these solvents proceeded in comparable yields with 35–42%. However, the reaction in DMSO gave **4a** in only 15% yield. Various aryl aldehydes with different substitution groups on the benzene rings were examined under the typical conditions. These results were summarized in Table 1. When the benzene ring of aryl aldehyde has an electron-withdrawing group, the desired product **4** was formed in a better yield. For example, exposure of 4-nitrobenzaldehyde and 1-phenylprop-2-yn-1-one with 2,4-pentanedione in the presence of PPh_3 (20 mol%) gave the corresponding product **4b** in 68% yield. The reaction with 4-cyanobenzaldehyde and 2-nitrobenzaldehyde gave the corresponding product **4f** and **4g** in 63% and 75% yields, respectively. Otherwise, the reaction time was prolonged to 12 hours and the desired product **4** was obtained in a lower yield if an electron-donating group was present on the benzene ring of aryl aldehyde. These results demonstrate that active aryl aldehyde with electron-withdrawing substituent is of great importance to the formation of product **4**.



Scheme 1

SYNLETT 2005, No. 19, pp 2990–2992
Advanced online publication: 27.10.2005
DOI: 10.1055/s-2005-918955; Art ID: W01305ST

Table 1 Reaction of Aldehydes and Acetylides with 1,3-Dicarbonyl Moieties in the Presence of PPh_3 (20 mol%)[a]

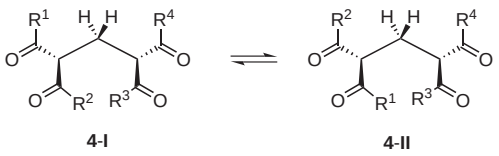
Entry	R^1	R^2	R^3	R^4	Time (h)	Product[b]	Yield (%)[c]
1	C_6H_5	C_6H_5	Me	Me	6	**4a**	41
2	4-$NO_2C_6H_4$	C_6H_5	Me	Me	6	**4b**	68
3	4-MeC_6H_4	C_6H_5	Me	Me	12	**4c**	28
4	4-$MeOC_6H_4$	C_6H_5	Me	Me	12	**4d**	15
5	4-ClC_6H_4	C_6H_5	Me	Me	12	**4e**	39
6	4-CNC_6H_4	C_6H_5	Me	Me	6	**4f**	63
7	2-$NO_2C_6H_4$	C_6H_5	Me	Me	6	**4g**	75
8	2-$NO_2C_6H_4$	Me	Me	Me	6	**4h**	59
9	4-$NO_2C_6H_4$	Me	Me	Me	6	**4i**	64
10	4-$NO_2C_6H_4$	$C_6H_5CH_2CH_2$	Me	Me	6	**4j**	57
11	4-$NO_2C_6H_4$	4-$MeOC_6H_4$	Me	Me	6	**4k**	42
12	4-$NO_2C_6H_4$	Me	$C_6H_5CH_2CH_2$	Me	6	**4l**	57
13	4-$NO_2C_6H_4$	Me	C_6H_5	Me	6	**4m**	79
14	4-$NO_2C_6H_4$	Me	C_6H_5	$CH_3CH_2CH_2$	6	**4n**	73
15	4-$NO_2C_6H_4$	Me	4-$MeOC_6H_4$	Me	6	**4o**	72
16	4-$NO_2C_6H_4$	Me	4-ClC_6H_4	Me	6	**4p**	70
17	4-$NO_2C_6H_4$	Me	C_6H_5	C_6H_5	6	**4q**	64
18	4-$NO_2C_6H_4$	Me	C_6H_5	OEt	6	**4r**	70
19	4-$NO_2C_6H_4$	Me	Me	OEt	10	**4s**	26

[a] In a typical reaction, aldehyde (0.3 mmol), acetylenic ketones (0.36 mmol) and 1,3-dicarbonyl compounds (0.36 mmol) were dissolved in a solution of CH_2Cl_2, then followed by PPh_3 (20 mol%).
[b] All compounds have been fully characterized by using ^1H NMR, ^{13}C NMR, IR spectroscopy, and mass spectrometry.
[c] Yields after purification by silica gel column chromatography.

This method was then extended to other acetylenic ketones. The reaction with 3-butyn-2-one and 5-phenylprop-2-yn-3-one gave the desired products **4i** and **4j** in 64% and 57% yields, respectively. However, an electron-donating group on the benzene ring of aromatic acetyenic ketone provided **4k** in a lower yield.

When this domino set of reaction was applied on other 1,3-diketones, they provided the corresponding products in comparable yields. Interestingly, aromatic 1,3-diketones gave the products in good yields. Substitution group on the benzene ring of aromatic 1,3-diketones has no obvious effect on the yields. On the other hand, aromatic β-ketoester also could undergo this domino reaction and provide the corresponding product **4r** in 70% yield. However, when ethyl acetoacetate was submitted to this reaction, the product **4s** was obtained in only 26% yield accompanied by an unidentified complicated mixture.

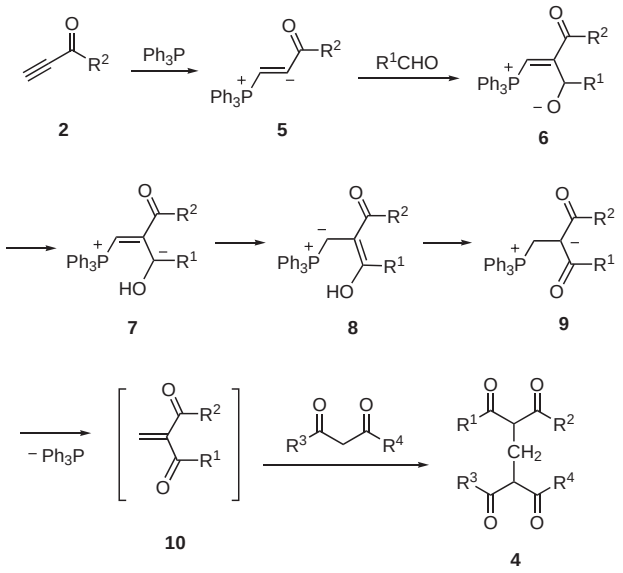
In all cases, compound **4** was present mainly in tetra-keto form. Only a trace amount of the enol form was observed from ^1H NMR and ^{13}C NMR spectra. For those compounds, which contain two chiral centers, a 1:1 mixture of diastereoisomers (**4-I** and **4-II**) was obtained. They were not separable by silica gel column chromatography (Scheme 2).



Scheme 2

A plausible mechanism to account for this domino reaction is presented in the Scheme 3. Triphenylphosphine acts as a nucleophilic promoter to initiate the reaction and produce zwitterionic intermediate **5**, which is actually an allenic enolate. The intermediate **5** adds to aldehyde to form the zwitterionic intermediate **6** and subsequent generation of **9** through two consecutive proton transfer.[13] PPh_3 is eliminated from the intermediate **9** to afford an alkylidine derivative **10**, which is then subjected to conjugate addition by 1,3-dicarbonyl compound to give product

4. On the other hand, the intermediate **5** could deprotonate the active methylene protons of 1,3-dicarbonyl compounds as well, then underwent α-addition to provide compound **3** as competing by-product.[11b] Actually, compound **10** was not found when the reaction was carried out in the absence of 1,3-dicarbonyl compound. The mechanistic details of this reaction need further investigation.



Scheme 3 A plausible mechanism in the reaction of aldehydes and acetylides with 1,3-dicarbonyl moieties catalyzed by PPh_3

In summary, we have described a new domino process catalyzed by triphenylphosphine, which supplies an efficient and facile way to synthesis multi-carbonyl compounds from simple and commercially available starting materials. The presented procedure leads to building blocks, potential intermediates of organic materials. Efforts are currently underway in our laboratories to elucidate the mechanistic details of this reaction and to disclose the scope and limitation of this reaction.

Acknowledgment

We thank the Natural Science Foundation of Anhui province (No. 050460302) for financial support.

References

(1) Carruthers, W.; Coldham, I. *Modern Methods of Organic Synthesis*; Cambridge University Press: Cambridge, **2004**, 1–71.
(2) Trost, B. M. *Science* **1991**, *254*, 1471.
(3) (a) Ho, T. L. *Tandem Organic Reactions*; Wiley-Interscience: New York, **1992**. (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.
(4) Dong, V. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 2448.
(5) For a recent account on phosphine-catalyzed reactions, see: (a) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535. (b) Grossman, R. B.; Comesse, S.; Rasane, R. M.; Hattori, K.; Delong, M. N. *J. Org. Chem.* **2003**, *68*, 871.
(6) For recent reports on phosphine-catalyzed reactions, see: (a) Zhu, X. F.; Schaffner, A. P.; Li, R. C.; Kwon, O. *Org. Lett.* **2005**, *7*, 2977. (b) Jung, C. K.; Wang, J. C.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 4118. (c) Du, Y.; Lu, X. *J. Org. Chem.* **2003**, *68*, 6463. (d) Zhu, X. F.; Lan, J.; Kwon, O. *J. Am. Chem. Soc.* **2003**, *125*, 4716. (e) Wang, J. C.; Ng, S. S.; Krische, M. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 5855. (f) Frank, S. A.; Mergott, D. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 2404. (g) Wang, L. C.; Luis, A. L.; Aqupiou, K.; Jang, H. Y.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 2402. (h) Lumbierres, M.; Moreno, M.; Vallribera, A. *Tetrahedron* **2002**, *58*, 4061. (i) Kuroda, H.; Tomita, I.; Endo, T. *Org. Lett.* **2003**, *5*, 129.
(7) (a) Trost, B. M.; Kazmaier, U. *J. Am. Chem. Soc.* **1992**, *114*, 7933. (b) Guo, C.; Lu, X. *J. Chem. Soc., Chem. Commun.* **1993**, 394. (c) Guo, C.; Lu, X. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1921.
(8) (a) Grossman, R. B.; Varner, M. A.; Skaggs, A. J. *J. Org. Chem.* **1999**, *64*, 340. (b) Grossman, R. B.; Comesse, S.; Ranse, R. M.; Hattori, K.; Delong, M. N. *J. Org. Chem.* **2003**, *68*, 871.
(9) (a) Trost, B. M.; Li, C. J. *J. Am. Chem. Soc.* **1994**, *116*, 7595. (b) Trost, B. M.; Li, C. J. *J. Am. Chem. Soc.* **1994**, *116*, 10819. (c) Zhang, C.; Lu, X. *Synlett* **1995**, 645. (d) Trost, B. M.; Dake, G. R. *J. Org. Chem.* **1997**, *62*, 5670. (e) Wang, J. C.; Ng, S. S.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 3682.
(10) (a) Du, Y.; Lu, X.; Yu, Y. *J. Org. Chem.* **2002**, *67*, 8901. (b) Zhang, C.; Lu, X. *J. Org. Chem.* **1995**, *60*, 2906. (c) Xu, Z.; Lu, X. *Tetrahedron Lett.* **1997**, *38*, 3461. (d) Zhu, G.; Chen, Z.; Jiang, Q.; Xiao, D.; Cao, P.; Zhang, X. *J. Am. Chem. Soc.* **1997**, *119*, 3836. (e) Xu, Z.; Lu, X. *J. Org. Chem.* **1998**, *63*, 5031. (f) Xu, Z.; Lu, X. *Tetrahedron Lett.* **1999**, *40*, 549.
(11) (a) Trost, B. M.; Dake, G. R. *J. Am. Chem. Soc.* **1997**, *119*, 7595. (b) Hanédanian, M.; Loreau, O.; Taran, F.; Mioskowski, C. *Tetrahedron Lett.* **2004**, *45*, 7035. (c) Hanédanian, M.; Loreau, O.; Sawicki, M.; Taran, F. *Tetrahedron* **2005**, *61*, 2287.
(12) **Typical Procedure.**
Benzaldehyde (0.3 mmol), 2,4-pentanedione (0.36 mmol) and phenyl acetylenic ketone (0.36 Lmol) were dissolved in 3 mL CH_2Cl_2. The mixture was cooled to 0 °C, and 20 mol% PPh_3 was added. The resulting mixture was warmed to r.t. and stirred for 6 h. After concentrated under reduced pressure the residue was purified by flash chromatography on silica gel (8:1 PE–EtOAc) to afford the corresponding pure product.
Compound **4a**: mp 126–128 °C (lit.[14] mp 126–127 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 7.2 Hz, 4 H), 7.58 (m, 2 H), 7.46 (m, 4 H), 5.38 (t, *J* = 6.8 Hz, 1 H), 3.97 (t, *J* = 6.8 Hz, 1 H), 2.51 (t, *J* = 6.8 Hz, 2 H), 2.27 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.4, 196.0, 135.6, 134.0, 129.1, 128.8, 64.8, 53.8, 29.8, 26.9 ppm. IR (neat): ν = 1725, 1696, 1671, 1596, 1580, 1253, 1181 cm^{-1}. HRMS (ESI): *m/z* calcd for $C_{21}H_{20}O_4$ $[M + Na]^+$: 359.1254; found: 359.1255.
Compound **3a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 16.66 (s, 1 H), 7.78 (m, 2 H), 7.53 (m, 1 H), 7.45 (m, 2 H), 6.08 (s, 1 H), 6.04 (s, 1 H), 2.01 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.4, 191.1 (2 C), 143.5, 136.5, 133.4 133.3, 132.8, 130.7, 111.5, 23.9 (2 C) ppm. IR (neat): ν = 1710, 1657, 1333, 1255, 1198 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{14}H_{14}O_3$ $[M^+]$: 230.0943; found: 230.0947.
(13) Li, C. Q.; Shi, M. *Org. Lett.* **2003**, *5*, 4273.
(14) Hellmann, H.; Dieterich, D. *Justus Liebigs Ann. Chem.* **1960**, *632*, 73.