A New Organocatalytic Process of Cyclotrimerization of Acetylenic Ketones Mediated by 2,4-Pentanedione

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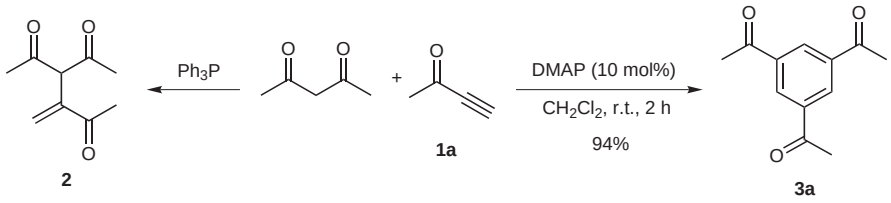
Abstract: A new organocatalytic process of cyclotrimerization of the aliphatic and aromatic acetylenic ketones was developed. The reaction catalyzed by DMAP in the presence of 2,4-pentanedione gave 1,3,5-trisubstituted benzenes in almost quantitative yields under very mild conditions. 2,4-Pentanedione was used as a co-catalyst to promote the reaction efficiently, particularly for aliphatic acetylenic ketones.

Key words: acetylenic ketones, DMAP, cyclotrimerization, 2,4-pentanedione

Cycloaddition of alkynes to generate benzene derivatives has been a key part of contemporary organic synthesis since the discovery of annulation of three acetylene molecules by Bertholet in 1866. Although transition-metal-catalyzed cyclotrimerization of alkynes has made great advances,[1] the regioselectivity of the process can still be troublesome.[2] Some metal-free catalytic methodologies for synthesis of 1,3,5-triaroylbenzenes have been developed from cyclotrimerization of aromatic acetylenic ketones.[3] Unfortunately, these reactions provide moderate yields in toluene under reflux conditions, and they cannot be applied to trimerization of aliphatic acetylenic ketones.[4] The rapid, efficient and regioselective generation of highly substituted benzenes is still a challenge in synthetic chemistry.[5]

1,3-Dicarbonyl derivatives constitute important synthetic intermediates, used as nucleophilic or electrophilic species in a variety of synthetic transformations.[6] Recently, we reported phosphine-catalyzed α-C-addition of 1,3-dicarbonyl compounds to acetylenic ketones.[7d] Moderate yields of the desired products **2** were obtained under our reaction conditions. In an effort to improve the yields, we utilized 10 mol% 4-dimethylaminopyridine (DMAP), in place of Ph_3P, as Lewis base to catalyze α-addition of 2,4-pentanedione to 3-butyn-2-one. It was surprising to find that 1,3,5-triacetylbenzene (**3a**) was obtained in 94% yield at room temperature after two hours (Scheme 1). 2,4-Pentanedione did not take part in the reaction. Actually, 2,4-pentanedione functioned as a co-catalyst to activate the cyclotrimerization of 3-butyn-2-one. To the best of our knowledge, this is the first example of β-dicarbonyl derivative used as organocatalyst to promote a reaction. Herein we describe the cyclotrimerization of acetylenic ketones catalyzed by DMAP in the presence of 2,4-pentanedione in almost quantitative yields under very mild conditions.

We first performed the reaction using different quantities of 2,4-pentanedione. Treatment of 3-butyn-2-one with 50 mol% 2,4-pentanedione and 10 mol% DMAP in CH_2Cl_2 for four hours at room temperature gave **3a** in 95% yield (entry 2, Table 1). When the reaction was carried out using 20 mol% 2,4-pentanedione, a little lower yield (80%) was obtained in prolonging the reaction time (18 h). However, no reaction took place when the mixture of 3-butyn-2-one and 10 mol% DMAP in the absence of 2,4-pentanedione was stirred for 24 hours. The results showed that 2,4-pentanedione was crucial for this cyclotrimerization, which might serve as a co-catalyst to activate the reaction. Then, several other β-dicarbonyl compounds, in place of 2,4-pentanedione, were tested in this reaction. It was found that they could also catalyze the reaction. But 2,4-pentanedione proved to be the most efficient additive to produce the target. For example, the use of 1-phenylbutane-1,3-dione **B** as a co-catalyst gave a low yield of **3a** (59%), along with a complex mixture of unidentified products. β-Keto ester **C** and ethyl acetoacetate **D** gave the desired product in comparable yields of 91% and 70%,



Scheme 1

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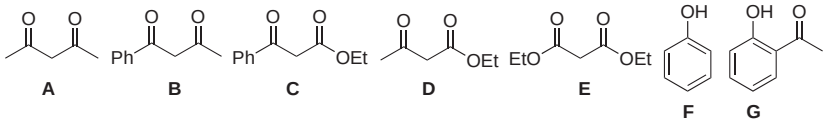
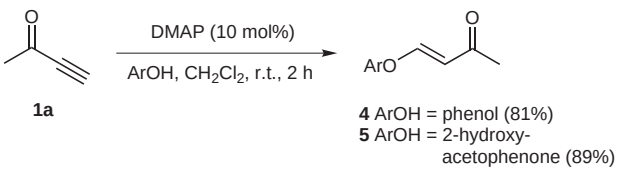
Table 1 Cyclotrimerization of 3-Butyn-2-one Catalyzed by a Lewis Base and an Additive



Entry	Catalyst	Additive (mol%)	Solvent	Time (h)	Yield (%)[a]
1	DMAP	A (100)	CH_2Cl_2	2	94
2	DMAP	A (50)	CH_2Cl_2	4	95
3	DMAP	A (20)	CH_2Cl_2	18	80
4	DMAP	–	CH_2Cl_2	24	0
5	DMAP	B (50)	CH_2Cl_2	4	59
6	DMAP	C (50)	CH_2Cl_2	6	91
7	DMAP	D (50)	CH_2Cl_2	6	70
8	DMAP	E (50)	CH_2Cl_2	12	92(53)[b]
9	DMAP	F (50)	CH_2Cl_2	2	81[c]
10	DMAP	G (50)	CH_2Cl_2	2	89[d]
11	DMAP	A (50)	Toluene	4	91
12	DMAP	A (50)	THF	4	93
13	DMAP	A (50)	DMF	4	76
14	DMAP	A (50)	DMSO	4	40
15	Pyridine	A (50)	CH_2Cl_2	4	67
16	Et_3N	A (50)	CH_2Cl_2	4	50
17	DABCO	A (50)	CH_2Cl_2	4	45
18	DBU	A (50)	CH_2Cl_2	4	0

[a] Yield after purification by silica gel chromatography.
[b] Reaction for 4 h.
[c] Yield of product **4**.
[d] Yield of product **5**.

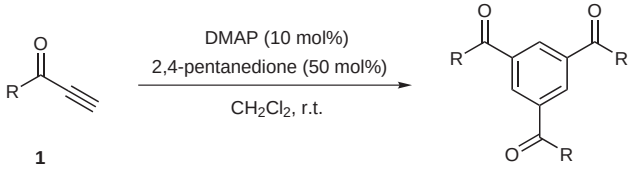
respectively. Although a longer reaction time was required to ensure the conversion in the presence of diethyl malonate **E**, the product **3a** was obtained in 92% yield after stirring 12 hours at room temperature. However, no desired product was obtained when malononitrile was used in the system. These results imply that the cyclotrimerization reaction proceeds smoothly in the presence of a β-dicarbonyl compound. Because β-dicarbonyl compounds exist predominantly as the enol tautomer in nonpolar solvents, it appears likely that an acidic proton of an enol hydroxyl group functions as Brønsted acid to catalyze the reaction. Recently, the use of small organic molecules as catalysts has attracted considerable attention in reaction methodology development. It was reported that phenol and BINOL worked as Brønsted acid to promote the Baylis–Hillman reaction of enones with aldehydes efficiently.[8] Unfortunately, when cyclotrimerization of 3-butyn-2-one was carried out using phenol **F** or 2-hydroxyacetophenone **G** as a Brønsted acid catalyst, no desired product **3a** was observed, but rather conjugate addition products **4** and **5** were obtained in 81% and 89% yields, respectively (Scheme 2). The choice of the solvent had an effect on the reaction. Toluene and THF were suitable solvents, and gave **3a** in 91% and 93% yields, respectively. The use of a more polar solvent, such as DMF and DMSO, gave the desired product in a relatively lower yield.



Scheme 2 Conjugate addition of ArOH to **1a** promoted by DMAP

The nature of the tertiary amine was shown to be important for the success of the reaction.[9] The reaction catalyzed by 10 mol% pyridine in the presence of 50 mol% 2,4-pentanedione as a co-catalyst could afford the desired product in 67% yield. When using Et_3N or 1,4-diazabicyclo[2,2,2]octane (DABCO) as a Lewis base catalyst, the desired product **3a** was obtained in a low yield, along with a complex mixture of unidentified products. However, when the reaction was carried out using DBU as a Lewis base, no product was found. As shown in Table 1, DMAP proved to be an extraordinary catalyst for the reaction, giving the product in excellent yield. Thus, we had established the optimal reaction conditions for this reaction using 10 mol% DMAP as a Lewis base catalyst and 50 mol% 2,4-pentanedione as a co-catalyst to perform the reaction in CH_2Cl_2 at room temperature.

Table 2 Cyclotrimerization of Acetylenic Ketones Catalyzed by DMAP and 2,4-Pentanedione



1 **3**

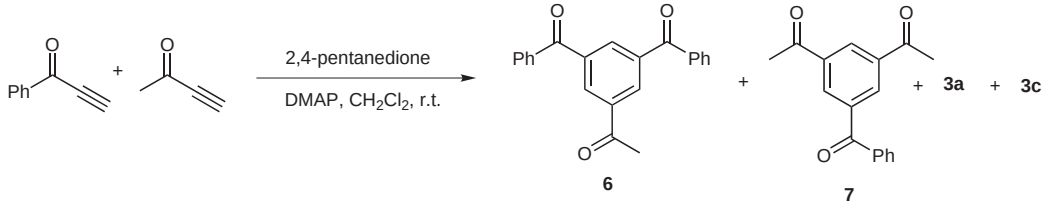
Entry	R	Time (h)	Product	Yield (%)[a]
1	Me	4	**3a**	95
2	$PhCH_2CH_2$	4	**3b**	96
3	Ph	2	**3c**	98
4	4-F-C_6H_4	2	**3d**	98
5	4-Cl-C_6H_4	2	**3e**	98
6	4-Br-C_6H_4	2	**3f**	97
7	4-NO_2-C_6H_4	2	**3g**	97
8	4-Me-C_6H_4	2	**3h**	98
9	4-MeO-C_6H_4	2	**3i**	98
10	1-Naphthyl	2	**3j**	95

[a] Yield after purification by silica gel column chromatography.

With these results in hand, a variety of acetylenic ketones was submitted to the reaction. These results were summarized in Table 2.[10] It was observed that all of the reactions proceeded smoothly under the mild conditions to afford the corresponding products in almost quantitative yields. The results exhibited the scope with respect to a range of aliphatic and aromatic acetylenic ketones. Aromatic acetylenic ketones showed higher reactivity in the cyclotrimerization reaction than aliphatic acetylenic ketones, and could produce 1,3,5-triaroylbenzenes in the absence of 2,4-pentanedione. For example, the reaction of 1-phenylprop-2-yn-1-one with 10 mol% DMAP in the absence of 2,4-pentanedione at room temperature for five hours could give the corresponding product **3c** in 29% yield. While **3c** was obtained in 98% yield when the reaction was carried out using 2,4-pentanedione as co-catalyst for two hours. Substitution of an electron-withdrawing group or an electron-donating group on the aromatic ring of the substrates resulted in no obvious effect on the reaction yields. But it should be noted that no product was observed when a β-substituted acetylenic ketone was submitted to this reaction under our typical conditions, which might be due to the steric effect. Therefore, we had developed an efficient and mild methodology for cyclotrimerization of terminal acetylenic ketones to synthesize 1,3,5-trisubstituted benzenes in excellent yields.

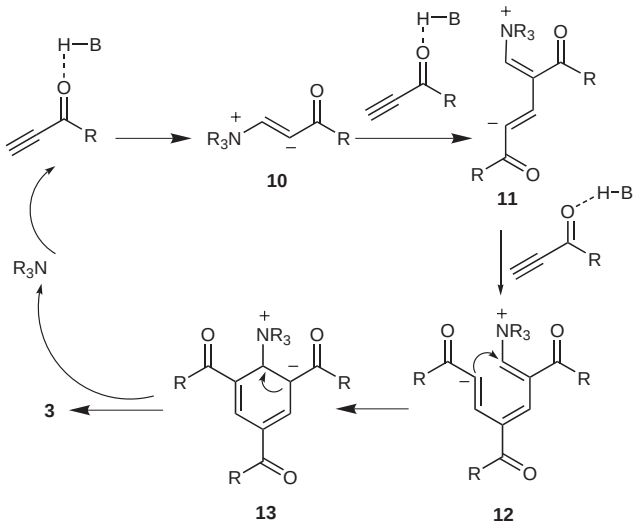
To extend the scope of this reaction, cross cyclotrimerization of two different acetylenic ketones was investigated (Scheme 3). The cross-reaction of but-3-yn-2-one (0.3 mmol) and 1-phenylprop-2-yn-1-one (0.3 mmol) performed at room temperature for four hours in the presence of 2,4-pentanedione (0.3 mmol) and DMAP (0.06 mmol) gave products **6** (0.071 mmol, 47%), **7** (0.038 mmol, 12%) and **3c** (0.028 mmol, 28%) along with a small amount of **3a**. Alternately, treatment of but-3-yn-2-one with two equivalents of 1-phenylprop-2-yn-1-one could provide products **6** (68%) as the major product, **7** (15%) and **3c** (14%).

On the base of our results, a plausible mechanism for the cyclotrimerization of acetylenic ketones is outlined in Scheme 4. DMAP acts as a nucleophilic promoter to initiate the reaction and produce zwitterionic intermediate **10**. The intermediate **10** adds to a second acetylenic ketone to form **11**, which is transferred into **12** by conjugate addition to a third acetylenic ketone. The intermediate **12** would then undergo cyclization, followed by elimination of DMAP to give product **3**. The role of 2,4-pentanedione may serve as Brønsted acid to activate the conjugate addition step during the reaction. The proton of the enolic hydroxyl group on the enol of 2,4-pentanedione may coordinate to the carbonyl oxygen of an acetylenic ketone,



6 **7**

Scheme 3 Cross-reaction of acetylenic ketones



Scheme 4 Plausible mechanism for the cyclotrimerization reaction

which is endowed with high acceptor capability in conjugate addition. The mechanistic details of this reaction need further investigation.

In summary, we have described a new and simple organocatalytic process of cyclotrimerization of acetylenic ketones. The reaction was catalyzed by DMAP as Lewis base in the presence of 2,4-pentanedione. Both aliphatic and aromatic acetylenic ketones reacted smoothly under mild conditions, affording 1,3,5-trisubstituted benzenes with excellent yields. 2,4-Pentanedione was used as co-catalyst to promote this annulation efficiently. Efforts are underway to ascertain the scope and limitations of this reaction.

Acknowledgment

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References and Notes

(1) (a) Shore, N. E. In *Comprehensive Organic Synthesis*, Vol. 5; Trost, B. M.; Fleming, I.; Paquette, L. A., Eds.; Pergamon: Oxford, **1991**, 1129–1162. (b) Grotjahn, D. B. In *Comprehensive Organometallic Chemistry II*, Vol. 12; Hegedus, L. S.; Abel, E. W.; Stone, F. G. A.; Wilkinson, G., Eds.; Pergamon: Oxford, **1995**, 741–770. (c) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (d) Frühauf, H.-W. *Chem. Rev.* **1997**, *97*, 523. (e) Yamamoto, Y.; Ishii, J.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2004**, *126*, 3712. (f) Meriwether, L. S.; Colthup, E. C.; Kennerly, G. W.; Reusch, R. N. *J. Org. Chem.* **1961**, *26*, 5155.

(2) (a) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901. (b) Ardizzoia, G. A.; Brenna, S.; LaMonica, G.; Maspero, A.; Masciocchi, N. *J. Organomet. Chem.* **2002**, *649*, 173. (c) Kotha, T.; Brahmachary, E.; Lahiri, K. *Eur. J. Org. Chem.* **2005**, 4741. (d) Xi, C.; Chen, C.; Lin, J.; Hong, X. *Org. Lett.* **2005**, *7*, 347. (e) Zhou, L.; Jiang, H.; Huang, J.; Tang, J. *Chin. J. Org. Chem.* **2006**, *26*, 1.

(3) (a) Pigge, F. C.; Zheng, Z. *Tetrahedron Lett.* **2001**, *42*, 8259. (b) Pigge, F. C.; Ghasedi, F.; Zheng, Z.; Rath, N. P.; Nichols, G.; Chickos, J. S. *J. Chem. Soc., Perkin Trans. 2* **2000**, 2458. (c) Pigge, F. C.; Ghasedi, F.; Rath, N. P. *Tetrahedron Lett.* **1999**, *40*, 8045. (d) Matsuda, K.; Nakamura, N.; Iwamura, H. *Chem. Lett.* **1994**, 1765. (e) Balasubramanian, K.; Selvaraj, S.; Venkataramani, P. S. *Synthesis* **1980**, 29. (f) Elghamry, I. *Synthesis* **2003**, 2301. (g) Pena, M. A.; Sestelo, J. P.; Sarandeses, L. A. *Synthesis* **2005**, 485. (h) Abdel-Khalik, M. M.; Elnagdi, M. H. *Synth. Commun.* **2002**, *32*, 159. (i) Almazroa, S.; Elnagdi, M. H.; El-Din, A. M. S. *J. Heterocycl. Chem.* **2004**, *41*, 267.

(4) Yang, J.; Verkade, G. *J. Am. Chem. Soc.* **1998**, *120*, 6834.

(5) (a) *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: Weinheim, **2002**. (b) *The Chemistry of Phenols*; Rappoport, Z., Ed.; Wiley-VCH: New York, **2003**.

(6) (a) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, *97*, 449. (b) Simon, C.; Constantieux, T.; Rodriguez, J. *Eur. J. Org. Chem.* **2004**, 4957. (c) Li, C. *Chem. Rev.* **2005**, *105*, 3095.

(7) (a) Hanédanian, M.; Loreau, O.; Sawicki, M.; Taran, F. *Tetrahedron* **2005**, *61*, 2287. (b) Trost, B. M.; Dake, G. R. *J. Am. Chem. Soc.* **1997**, *119*, 7595. (c) Hanédanian, M.; Loreau, O.; Taran, F.; Mioskowski, C. *Tetrahedron Lett.* **2004**, *45*, 7035. (d) Xue, S.; Zhou, Q.; Zheng, X. *Synth. Commun.* **2005**, *35*, 3027.

(8) (a) Yamada, Y. M. A.; Ikegami, S. *Tetrahedron Lett.* **2000**, *41*, 2165. (b) McDougal, N. T.; Schaus, S. E. *J. Am. Chem. Soc.* **2003**, *125*, 12094. (c) Shi, M.; Liu, Y. H. *Org. Biomol. Chem.* **2006**, *4*, 1468.

(9) For selected recent reactions catalyzed by amines, see: (a) Wang, Y.; Cui, S.; Lin, X. *Org. Lett.* **2006**, *8*, 1241. (b) Sonye, J. P.; Koide, K. *Org. Lett.* **2006**, *8*, 199. (c) Shi, Y.; Shi, M. *Org. Lett.* **2005**, *7*, 3057. (d) Tejedor, D.; Santos-Exposito, A.; Gonzalez-Cruz, D.; Marrero-Tellado, J. J.; Garcia-Tellado, F. *J. Org. Chem.* **2005**, *70*, 1042. (e) Bella, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 5672. (f) Li, C.; Shi, M. *Org. Lett.* **2003**, *5*, 4273.

(10) **Typical Procedure.**
A round-bottomed flask, equipped with a stirring bar, was charged with 2,4-pentanedione (0.15 mmol) and acetylenic ketone (0.3 mmol) dissolved in CH_2Cl_2 (2 mL) followed by DMAP (0.03 mmol). The reaction was run at r.t. for the indicated time (monitored by TLC). The reaction was concentrated under reduced pressure on a rotary evaporator and purified by silica gel chromatography using PE–EtOAc (10:1 to 3:1).
Compound **3a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.63 (s, 3 H), 2.64 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.7, 138.0, 131.8, 26.9 ppm. IR (KBr): ν = 1690, 1227 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{12}H_{12}O_3$ [M]$^+$: 204.0786; found: 204.0791.
Compound **3b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.56 (s, 3 H), 7.25–7.10 (m, 15 H), 3.31 (t, *J* = 7.5 Hz, 6 H), 3.03 (t, *J* = 7.5 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.9, 140.8, 137.8, 131.3, 128.7, 128.6, 126.4, 40.8, 30.1 ppm. IR (KBr): ν = 1694, 1162 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{33}H_{30}O_3$ [M]$^+$: 474.2195; found: 474.2192.
Compound **6**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.49 (d, *J* = 1.5 Hz, 2 H), 8.29 (d, *J* = 1.5 Hz, 1 H), 7.76 (d, *J* = 7.6 Hz, 4 H), 7.57–7.54 (m, 2 H), 7.47–7.42 (m, 4 H), 2.63 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.4, 193.9, 137.4, 136.4, 135.4, 133.8, 132.2, 131.5, 129.0, 127.6, 25.8 ppm. IR (KBr): ν = 1691, 1662, 1242 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{22}H_{16}O_3$ [M]$^+$: 328.1099; found: 328.1092.