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Triple condensation of aryl methyl ketones catalyzed by amine and trifluoroacetic acid: straightforward access to 1,3,5-triarylbenzenes under mild conditions

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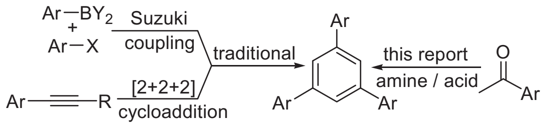
ABSTRACT

An efficient triple condensation reaction of aryl methyl ketones catalyzed by ethylenediamine and trifluoroacetic acid was reported. A broad scope of 1,3,5-triarylbenzenes was obtained in good to excellent yields. The reaction provides a novel and practical approach to access organic materials of polycyclic aromatic hydrocarbons under mild conditions.

Polycyclic aromatic hydrocarbons (PAHs) have attracted much attention due to their potential application in organic semiconductors, nanomaterials, and photovoltaics.[1,2] As key building blocks for the preparation of PAHs, the 1,3,5-triarylbenzenes have also been used for developing organic light emitting diodes (OLEDs)[3] and synthesis of dendrimers[4] and fullerene fragments.[5] Traditionally, 1,3,5-triarylbenzenes were synthesized via acid-catalyzed triple condensation of aryl methyl ketones,[6] Suzuki coupling reaction,[7] and [2+2+2] cycloaddition of arylacetylenes(arylethynes)[8] (Scheme 1). It is well known that ketones and aldehydes can be activated through iminium or enamine with amines. Therefore, we envisaged that amines could catalyze the triple condensation of aryl methyl ketones to accomplish 1,3,5-triarylbenzenes. In 1936, Clapp and Morton realized the cyclotrimerization of three aryl methyl ketones using catalytic amount of aniline hydrochloride in aniline as the solvent to form the products in low yields (18–23%).[9] To our knowledge, a general and efficient process has not been reported for amine/acid-catalyzed triple condensation of aryl methyl ketones. Herein, we wish to report, for the first time, an efficient triple condensation reaction catalyzed by ethylenediamine and trifluoroacetic acid (TFA), which is sustainable for aryl methyl ketones of various electronic properties.

Initially, we investigated primary, secondary, and tertiary amines for their ability to promote the triple condensation reaction using acetophenone as a substrate and trifluoroacetic acid (TFA) as an additive at reflux in benzene (Table 1). The reaction was found to proceed in low yield (34%) with aniline (entry 1). There was no remarkable improvement in yield when increasing aniline loading or using substituted anilines with electron-donating group or electron-withdrawing group (entries 2 and 3). To our delight, when ethylenediamine was used as catalyst, acetophenone was converted into the desired product in good yield (70%) (entry 4), and *o*-phenylenediamine as catalyst to give moderate yield (57%) (entry 5). In contrast, *n*-butylamine, piperidine, diisopropylamine, and triethylamine were almost inactive for the triple condensation reaction (entries 6–9). Notably, the desired 1,3,5-triphenylbenzene was not observed in the absence of ethenediamine or TFA (entries 10 and 11). Then using ethenediamine as catalyst and TFA as additive, a range of solvents were examined, polar solvents were



Scheme 1. Synthesis of 1,3,5-triarylbenzene.

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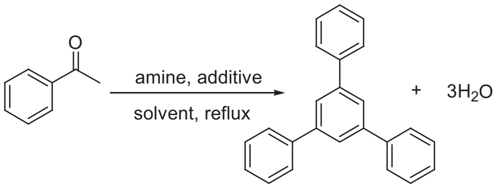
Table 1
Optimizing reaction conditions[a]



Entry	Amine	Additive	Solvent	Temp (°C)	Yield[b] (%)
1	Aniline	TFA	Benzene	80	34[c]
2	4-Methoxyaniline	TFA	Benzene	80	42
3	4-Nitroaniline	TFA	Benzene	80	35
4	Ethylenediamine	TFA	Benzene	80	70
5	*o*-Phenylenediamine	TFA	Benzene	80	57
6	*n*-Butylamine	TFA	Benzene	80	<5
7	Piperidine	TFA	Benzene	80	<5
8	Diisopropylamine	TFA	Benzene	80	<5
9	Et_3N	TFA	Benzene	80	NR
10	—	TFA	Benzene	80	NR
11	Ethylenediamine	—	Benzene	80	NR
12	Ethylenediamine	TFA	Toluene	110	19
13	Ethylenediamine	TFA	CH_3OH	64	Trace
14	Ethylenediamine	TFA	C_2H_5OH	78	<5
15	Ethylenediamine	TFA	CH_3CN	81	15
16[d]	**Ethylenediamine**	**TFA**	$\mathbf{CH_3NO_2}$	**101**	**87**
17	Ethylenediamine	TFA	THF	66	NR
18	Ethylenediamine	TFA	EtOAc	77	NR
19	Ethylenediamine	TFA	DMF	152	NR
20	Ethylenediamine	TFA	DMSO	189	NR
21	Ethylenediamine	AcOH	CH_3NO_2	101	29
22	Ethylenediamine	Formic acid	CH_3NO_2	101	NR
23	Ethylenediamine	Oxalic acid	CH_3NO_2	101	9
24	Ethylenediamine	Benzoic acid	CH_3NO_2	101	26
25	Ethylenediamine	PTSA	CH_3NO_2	101	42

TFA: trifluoroacetic acid; PTSA: *p*-toluenesulfonic acid.

[a] Reaction conditions: **1a** (1.5 mmol), amine (0.3 mmol), and additive (0.6 mmol) in solvent (1.5 mL) reacted for 60 h at corresponding temperature.

[b] Isolated yield.

[c] Aniline increased to 0.6 mmol, the yield is 35%.

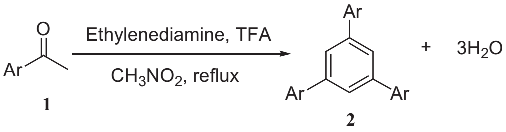
[d] Reacted for 48 h.

unsuitable for the condensation reaction, while CH_3NO_2 gave the best yield (87%) (entries 12–20). For additive, weaker acids, such as acetic acid, formic acid, oxalic acid, and benzoic acid, were not efficient to promote the condensation reaction, while *p*-toluenesulfonic acid (PTSA) gave moderate yield (42%) (entries 21–25).

With the optimal reaction conditions in hand, we then examined the substrates scope, and the results are summarized in Table 2. Various substituted aromatic methyl ketones were examined. Both electron-withdrawing and electron-donating groups on the aromatic ring were tolerated, yielding the desired products in moderate to high yields (60–93%) (entries 1–10). 2-Furyl and 2-thiophene methyl ketones gave the corresponding products in 46% and 90% yields, respectively, (entries 11 and 12). Furthermore, acetylnaphthalenes were found to serve as suitable substrates for the triple condensation reaction and afforded good yields (entries 13 and 14).

A plausible mechanism for ethylenediamine catalyzed triple condensation of aryl methyl ketones for preparation of 1,3,5-triarylbenzenes is depicted in Scheme 2. Aryl methyl ketones react with ethylenediamine and TFA to form intermediates iminium (**3**). Intramolecular addition affords *β*-amino iminium (**4**) which releases an amine, followed by tautomerization to give conjugated diene (**6**). Diene (**6**) condenses with aryl methyl ketone to give iminium (**7**), which is subjected to similar intramolecular addition, elimination and tautomerization to obtain conjugated triene (**10**), then 6π-electrocyclization and elimination of ethylenediamine catalyst to produce 1,3,5-triarylbenzene.

Table 2
Scope of ethylenediamine and TFA catalyzed triple condensation of aryl methyl ketones[a]

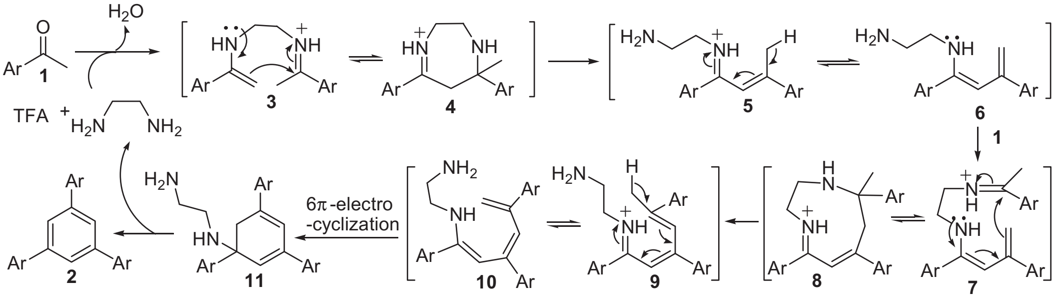


Entry	Ar	Time (h)	Mp (lit.[c]) (°C)	Yield[b] (%)
1	Ph (**2a**)	48	171–173 (170–172)	87
2	4-FC_6H_4 (**2b**)	36	241–243 (238–240)	92
3	4-ClC_6H_4 (**2c**)	36	246–248 (246–248)	90
4	4-BrC_6H_4 (**2d**)	48	260–262 (260–261)	69
5	4-IC_6H_4 (**2e**)	48	264–265 (262–263)	60
6	4-MeC_6H_4 (**2f**)	36	177–178 (179–180)	92
7	4-$AllylOC_6H_4$ (**2g**)	36	83–84 (83–85)	83
8	2-ClC_6H_4 (**2h**)	36	161–163 (162–164)	72
9	2-BrC_6H_4 (**2i**)	48	161–163 (159–160)	61
10	3-BrC_6H_4 (**2j**)	36	170–171 (167–168)	93
11	2-Furyl (**2k**)	24	126–128 (125–126)	46
12	2-Thiophene (**2l**)	24	158–159 (156–158)	90
13	1-Naphthalene (**2m**)	48	156–157 (155–156)	72
14	2-Naphthalene (**2n**)	48	222–223 (222–223)	66
15	2-PhC_6H_4 (**2o**)	4d	211–212 (—)	90

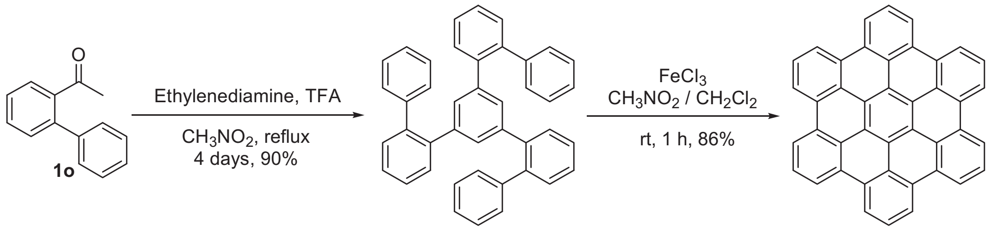
[a] Reaction conditions: **1** (1.5 mmol), ethylenediamine (0.3 mmol), and TFA (0.6 mmol) in CH_3NO_2 (1.5 mL) at 101 °C.

[b] Isolated yield.

[c] Mp in parentheses was reported in literature.



Scheme 2. Plausible mechanism for primary amine catalyzed triple condensation of aryl methyl ketones.



1o **2o** **HBC**

Scheme 3. Preparation of hexabenzocoronene (HBC).

The present reaction is potentially useful in the synthesis of organic materials. For example, in the presence of ethylenediamine and TFA, 2-phenyl-acetophenone (**1o**) was refluxed to give the corresponding triple condensation product (**2o**) in excellent yield (entry 15, Table 2 and Scheme 3). Compound **2o** was readily cyclodehydrogenated with $FeCl_3$ in a mixture of dichloromethane-nitromethane to obtain hexabenzocoronene (HBC),[10c] which has been the focus of considerable research for materials chemistry, especially, serving as useful organic semiconductors in electronic and optoelectronic devices.[10]

In summary, we have developed the general and efficient triple condensation reaction of aryl methyl ketones catalyzed by ethylenediamine and trifluoroacetic acid. The reaction proceeds in a broad range of substrates to afford 1,3,5-triarylbenzenes under mild conditions in good yields. A plausible mechanism was proposed. The reported method represents a novel and practical approach to access organic materials of polycyclic aromatic hydrocarbons. Further investigations on the application of the condensation reaction are in progress.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.03.008.

References and notes

1. For recent reviews of PAHs, see: (a) Li, C.; Liu, M.; Pschirer, N. G.; Baumgarten, M.; Müllen, K. *Chem. Rev.* **2010**, *110*, 6817–6855; (b) Wu, J.; Pisula, W.; Müllen, K. *Chem. Rev.* **2007**, *107*, 718–747; (c) Coropceanu, V.; Cornil, J.; Da Silva Filho, D. A.; Olivier, Y.; Silbey, R.; Brédas, J-L. *Chem. Rev.* **2007**, *107*, 926–952; (d) Grimsdale, A. C.; Müllen, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 5592–5629.
2. (a) Uribe-Romo, F. J.; Doonan, C. J.; Furukawa, H.; Oisaki, K.; Yaghi, O. M. *J. Am. Chem. Soc.* **2011**, *133*, 11478–11481; (b) Terazono, Y.; Kodis, G.; Bhushan, K.; Zaks, J.; Madden, C.; Moore, A. L.; Moore, T. A.; Fleming, G. R.; Gust, D. *J. Am. Chem. Soc.* **2011**, *133*, 2916–2922; (c) Dash, B. P.; Satapathy, R.; Gaillard, E. R.; Norton, K. M.; Maguire, J. A.; Chug, N.; Hosmane, N. S. *Inorg. Chem.* **2011**, *50*, 5485–5493; (d) Jin, W.; Yamamoto, Y.; Fukushima, T.; Ishii, N.; Kim, J.; Kato, K.; Takata, M.; Aida, T. *J. Am. Chem. Soc.* **2008**, *130*, 9434–9440; (e) Matsumura, S.; Hlil, A. R.; Lepiller, C.; Gaudet, J.; Guay, D.; Shi, Z.; Holdcroft, S.; Hay, A. S. *Macromolecules* **2008**, *41*, 281–284; (f) Xu, W-Z.; Huang, Z-T.; Zheng, Q-Y. *Tetrahedron Lett.* **2008**, *49*, 4918–4921; (g) Bao, C.; Jin, M.; Lu, R.; Song, Z.; Yang, X.; Song, D.; Xu, T.; Liu, G.; Zhao, Y. *Tetrahedron* **2007**, *63*, 7443–7448; (h) Bao, C.; Lu, R.; Jin, M.; Xue, P.; Tan, C.; Xu, T.; Liu, G.; Zhao, Y. *Chem. Eur. J.* **2006**, *12*, 3287–3294; (i) Zhang, W.; Cao, X-Y.; Zi, H.; Pei, J. *Org. Lett.* **2005**, *7*, 959–962; van de (j) Craats, A. M.; Stutzmann, N.; Bunk, O.; Nielsen, M. M.; Watson, M.; Müllen, K.; Chanzy, H. D.; Sirringhaus, H.; Friend, R. H. *Adv. Mater.* **2003**, *15*, 495–499.
3. (a) Kotha, S.; Kashinath, D.; Kumar, S. *Tetrahedron Lett.* **2008**, *49*, 5419–5423; (b) Luo, J.; Zhou, Y.; Niu, Z-Q.; Zhou, Q-F.; Ma, Y.; Pei, J. *J. Am. Chem. Soc.* **2007**, *129*, 11314–11315; (c) Pang, J.; Marcotte, E. J-P.; Seward, C.; Brown, R. S.; Wang, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 4042–4045.
4. (a) He, Q.; Haung, H.; Yang, J.; Lin, H.; Bai, F. *J. Mater. Chem.* **2003**, *13*, 1085–1089; (b) Brunel, J.; Ledoux, I.; Zyss, J.; Blanchard-Desce, M. *Chem. Commun.* **2001**, *10*, 923–924.
5. (a) Vivekanand, P. A.; Balakrishnan, T. *Appl. Catal. A* **2009**, *364*, 27–34; (b) Gómez-Lor, B.; Echavarren, A. M. *Org. Lett.* **2004**, *6*, 2993–2996; (c) Gómez-Lor, B.; González-Cantalapiedra, E.; Ruiz, M.; de Frutos, Ó.; Cárdenas, D. J.; Santos, A.; Echavarren, A. M. *Chem. Eur. J.* **2004**, *10*, 2601–2608; (d) Mongin, O.; Brunel, J.; Porrès, L.; Blanchard-Desce, M. *Tetrahedron Lett.* **2003**, *44*, 2813–2816.
6. For select examples with acid-catalyzed triple condensation reaction, see: (a) Yang, J-X.; Tao, X-T.; Yuan, C. X.; Yan, Y. X.; Wang, L.; Liu, Z.; Ren, Y.; Jiang, M. H. *J. Am. Chem. Soc.* **2005**, *127*, 3278–3279; (b) Juárez-Pérez, E. J.; Viñas, C.; Teixidor, F.; Santillan, R.; Farfán, N.; Abreu, A.; Yépez, R.; Núñez, R. *Macromolecules* **2010**, *43*, 150–159; (c) Cao, X-Y.; Liu, X-H.; Zhou, X-H.; Zhang, Y.; Jiang, Y.; Cao, Y.; Cui, Y-X.; Pei, J. *J. Org. Chem.* **2004**, *69*, 6050–6058; (d) Li, B. Z.; Fung, H. S.; Song, X.; Chan, K. S. *Organometallics* **2011**, *30*, 1984–1990; (e) Kumar, A.; Dixit, M.; Singh, S. P.; Raghunandan, R.; Maulik, P. R.; Goel, A. *Tetrahedron Lett.* **2009**, *50*, 4335–4339; (f) Xia, H.; He, J.; Peng, P.; Zhou, Y.; Li, Y.; Tian, W. *Tetrahedron Lett.* **2007**, *48*, 5877–5881; (g) Jing, X.; Xu, F.; Zhu, Q.; Ren, X.; Yan, C.; Wang, L.; Wang, J. *Synth. Commun.* **2005**, *35*, 3167–3171; (h) Ono, F.; Ishikura, Y.; Tada, Y.; Endo, M.; Sato, T. *Synlett* **2008**, 2365–2367; (i) Phatangare, K.; Padalkar, V.; Mhatre, D.; Patil, K.; Chaskar, A. *Synth. Commun.* **2009**, *39*, 4117–4121; (j) Hu, H.; Zhang, A.; Ding, L.; Lei, X.; Zhang, L. *J. Chem. Res.* **2007**, *12*, 720–721.
7. For select examples with Suzuki coupling reaction: (a) Kao, M-T.; Chen, J-H.; Chu, Y-Y.; Tseng, K-P.; Hsu, C-H.; Wong, K-T.; Chang, C-W.; Hsu, C-P.; Liu, Y-H. *Org. Lett.* **2011**, *13*, 1714–1717; (b) Huang, H.; Fu, Q.; Zhuang, S.; Liu, Y.; Wang, L.; Chen, J.; Ma, D.; Yang, C. *J. Phys. Chem. C* **2011**, *115*, 4872–4878; (c) Wren, E.

J.; Wang, X.; Farlow, A.; Lo, S-C.; Burn, P. L.; Meredith, P. *Org. Lett.* **2010**, *12*, 4338–4340; (d) Yan, H.; Wong, C.; Chianese, A. R.; Luo, J.; Wang, L.; Yin, J.; Zhong, C-J. *Chem. Mater.* **2010**, *22*, 5918–5928; (e) Schnobrich, J. K.; Lebel, O.; Cychosz, K. A.; Dailly, A.; Wong-Foy, A. G.; Matzger, A. J. *J. Am. Chem. Soc.* **2010**, *132*, 13941–13948; (f) Zhang, X.; Quan, Y.; Cui, Z.; Chen, Q.; Ding, J.; Lu, J. *Eur. J. Org. Chem.* **2010**, 2295–2303; (g) Su, S-J.; Takahashi, Y.; Chiba, T.; Takeda, T.; Kido, J. *Adv. Funct. Mater.* **2009**, *19*, 1260–1267; (h) Mora, M.; Jiménez-Sanchidrián, C.; Ruiz, J. R. *Appl. Organomet. Chem.* **2008**, *22*, 122–127; (i) Noguchi, H.; Shioda, T.; Chou, C-M.; Suginome, M. *Org. Lett.* **2008**, *10*, 377–380; (j) Bonvallet, P. A.; Breitkreuz, C. J.; Kim, Y. S.; Todd, E. M.; Traynor, K.; Fry, C. G.; Ediger, M. D.; McMahon, R. J. *J. Org. Chem.* **2007**, *72*, 10051–10057; (k) Kotha, S.; Kashinath, D.; Lahiri, K.; Sunoj, R. B. *Eur. J. Org. Chem.* **2004**, 4003–4013.

8. (a) Ciammaichella, A.; Leoni, A.; Tagliatesta, P. *New J. Chem.* **2010**, *34*, 2122–2124; (b) Geny, A.; Agenet, N.; Iannazzo, L.; Malacria, M.; Aubert, C.; Gandon, V. *Angew. Chem., Int. Ed.* **2009**, *48*, 1810–1813; (c) Hilt, G.; Hengst, C.; Hess, W. *Eur. J. Org. Chem.* **2008**, *13*, 2293–2297; (d) Goswami, A.; Ito, T.; Okamoto, S. *Adv. Synth. Catal.* **2007**, *349*, 2368–2374; (e) Joosten, A.; Soueidan, M.; Denhez, C.; Harakat, D.; Hélion, F.; Namy, J-L.; Vasse, J-L.; Szymoniak, J. *Organometallics* **2008**, *27*, 4152–4157; (f) Lin, Y-Y.; Tsai, S-C.; Yu, S. J. *J. Org. Chem.* **2008**, *73*, 4920–4928; (g) Yoshida, K.; Morimoto, I.; Mitsudo, K.; Tanaka, H. *Tetrahedron* **2008**, *64*, 5800–5807; (h) Yoshida, K.; Morimoto, I.; Mitsudo, K.; Tanaka, H. *Chem. Lett.* **2007**, *36*, 998–999; (i) Sierra, M. A.; Torres, M. R.; De la Torre, M. C.; Álvaro, E. *J. Org. Chem.* **2007**, *72*, 4213–4219; (j) Cadierno, V.; García-Garrido, S. E.; Gimeno, J. *J. Am. Chem. Soc.* **2006**, *128*, 15094–15095; (k) Morohashi, N.; Yokomakura, K.; Hattori, T.; Miyano, S. *Tetrahedron Lett.* **2006**, *47*, 1157–1161; (l) Kakeya, M.; Fujihara, T.; Kasaya, T.; Nagasawa, A. *Organometallics* **2006**, *25*, 4131–4137; (m) Li, J.; Jiang, H.; Chen, M. *J. Org. Chem.* **2001**, *66*, 3627–3629; (n) Fu, Y-S.; Yu, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 437–440; (o) Tagliatesta, P.; Elakkari, E.; Leoni, A.; Lembo, A.; Cicero, D. *New J. Chem.* **2008**, *32*, 1847–1849.
9. (a) Clapp, D. B.; Morton, A. A. *J. Am. Chem. Soc.* **1936**, *58*, 2172; (b) For similar aniline hydrochloride catalyzed triple condensation reaction of aryl methyl ketones, also see: Aslam, M.; Basinger, W. U.S. Patent 5,300,698, 1994.
10. (a) Murphy, F. A.; Draper, S. M. *J. Org. Chem.* **2010**, *75*, 1862–1870; (b) Wadumethrige, S. H.; Rathore, R. *Org. Lett.* **2008**, *10*, 5139–5142; (c) Feng, X.; Wu, J.; Enkelmann, V.; Müllen, K. *Org. Lett.* **2006**, *8*, 1145–1148; (d) Dou, X.; Yang, X.; Bodwell, G. J.; Wagner, M.; Enkelmann, V.; Müllen, K. *Org. Lett.* **2007**, *9*, 2485–2488.