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Solvent-free $MeSO_3H$-promoted cyclotrimerization of acetophenones, effects of halogen and methoxy substituents on the reaction

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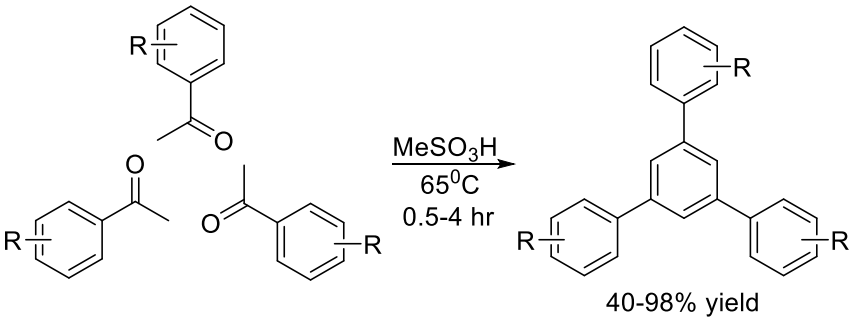
Abstract

A solvent free $MeSO_3H$-catalysed cylotrimerization of acetophenone and its aromatic substituted derivatives to give 1,3,5-triphenylbenzenes is described. Acetophenones with halogen substituents on the aromatic ring gave the corresponding triphenylbenzenes in 79-98% yield while the acetophenones with methoxy substituents gave the corresponding products in 40-48%. The cyclotrimerization of acetophenones with electron-withdrawing halogen substituents proceeded at a rate three times slower than the reaction of acetophenone while those with electron-donating methoxy substituents proceeded eight times slower.



Keywords: Acetophenone, cyclotrimerization, 1,3,5-triphenylbenzene, methanesulphonic acid

Introduction

As part of a broad interest in flavonoids, we have been investigating the use of enolate and related chemistry in the synthesis of chromenes.[1-3] Within this context, while investigating the three component $MeSO_3H$-catalysed reaction of 2-hydroxybenzaldehyde, acetophenone and diethylamine as a enamine-imminium salt synthetic route to 4-amino-2-phenylchromene, a complex mixture of products was detected. Gratifyingly, it was possible to isolate 1,3,5-triphenylbenzene from the reaction mixture in 22% yield. On the basis of some precedent,[4] it was obvious that the 1,3,5-triphenylbenze product was due to the cyclotrimerization of acetophenone.

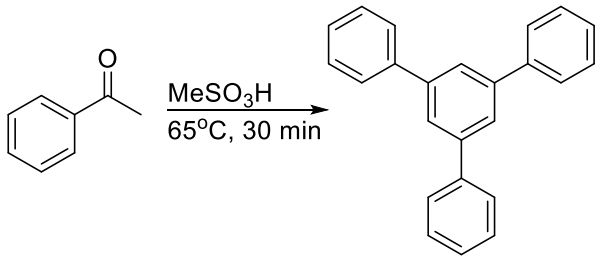
Interest in studying 1,3,5-triphenylbenzenes in recent years is due to their thermal and photochemical stability and their conjugated π-electron rich characteristic.[5] These compounds have therefore found application in photoluminescent chemosensors,[5] and light-emitting diodes.[6] Further, 1,3,5-triphenylbenzenes have been found to be effective inhibitors of amyloid fibril formation.[7]

Herein is a report of the study of the solvent-free $MeSO_3H$-promoted cyclotrimerization of acetophenone and investigation of the effect of electron withdrawing halo- and electron donating methoxy-aromatic substituents on this reaction.

Results and Discussion

When acetophenone (**1**) was treated with $MeSO_3H$ and the mixture was heated at 65 °C for 30 minutes, cyclotrimerization occurred to give 1,3,5-triphenylbenzene (**2**) in 95% yield, scheme 1. Gao and co-workers recently reported a related solvent free p-TsOH-catalysed cyclotrimerization of acetophenone at 140 °C to give cyclotrimer **2** in 88% yield.[4] The conditions for the methods described here are milder and the reaction gave a significantly higher yield of cyclotrimer **2** when compared to the literature method.

The structure of **2** was established on the basis of mass spectrometry and NMR experiments. In addition, the product gave good crystals and its structure was confirmed by single crystal XRD analysis, figure 1.



1 **2** (95%)

Scheme 1. Cyclotrimerization of acetophenone (**1**).

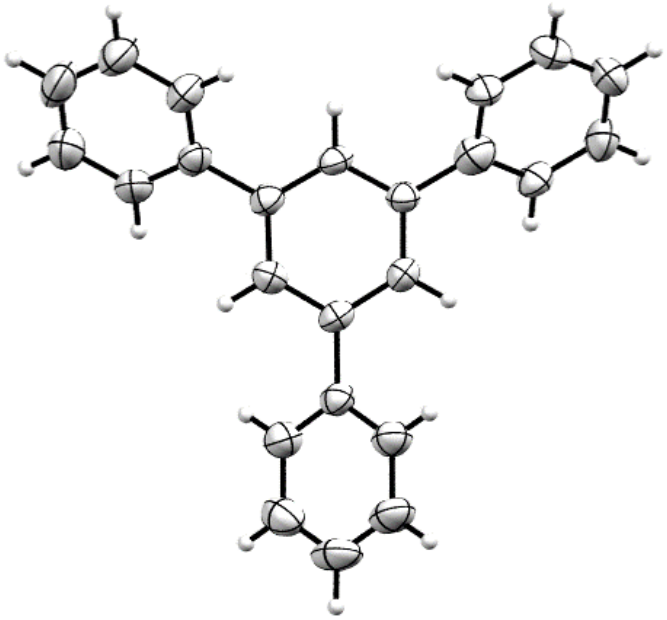
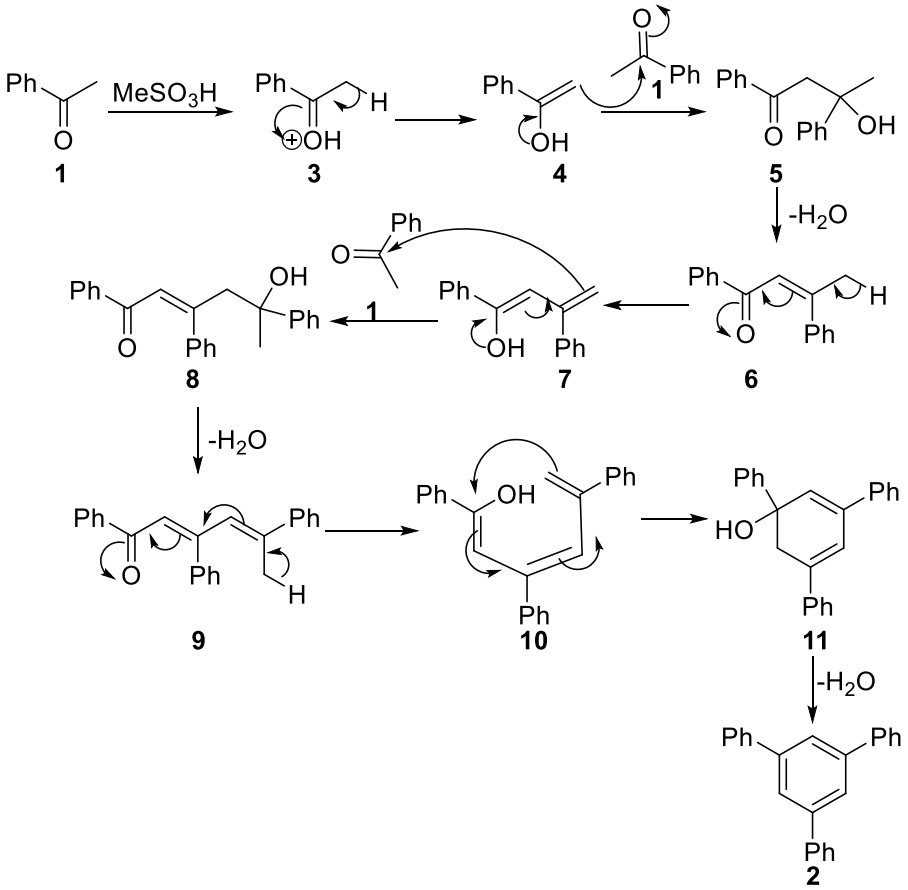


Figure 1. XRD crystal structure of **2.**

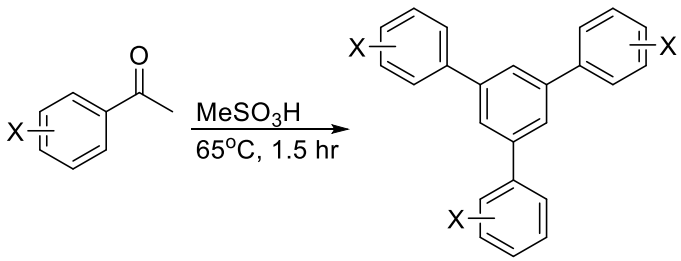
It is instructive to outline the possible mechanism of the cyclotrimerization of acetophenone. First, acetophenone (**1**) undergoes an acid-catalysed enolisation reaction to give enol **4**. Enol **4** then reacts with another molecule of **1** to give β-hydroxyketone **5** which loses water to give conjugated ketone **6**. Next, enolisation of **6** proceeds to give enol **7** which in turn reacts with a third molecule of **1** to give 5-hydroxyketone **8**. A dehydration reaction occurs to give 2,4-dienoketone **9** which undergoes an enolisation reaction to give enol **10**. Enol **10** is a conjugated 6π electron system which undergoes an electrocyclic reaction to give 5-hydroxycylodiene **11**. Finally, **11** undergoes a dehydration reaction to give the product **2**, Scheme 2.

Electron-withdrawing groups on the aromatic ring of acetophenone increase the electrophilicity of the carbonyl carbon atom and the acidity of the α-hydrogen atoms, hence increase the rate of the enolisation and condensation reactions in the mechanism. It was therefore anticipated that the rate of the cylotrimerization reactions of acetophenones with electron-withdrawing halogens will be faster. However, when a mixture of 2-chloroacetophenone (**12**) and $MeSO_3H$ was heated, it took 1.5 hours for the reaction to come to completion and the corresponding cyclotrimer **13** was isolated in 98% yield, scheme 3. It was assumed that steric hindrance due to the nearness of the chloro-group to the carbonyl functionality was responsible for the extended reaction time. The structure of **13** was confirmed by XRD analysis, figure 2.



Scheme 2. Possible mechanism of the cyclotrimerization of acetophenone (**1**).

Interestingly, and perhaps somewhat surprisingly, when 3-bromoacephenone (**14**) was treated with $MeSO_3H$ at elevated temperature, the cyclotrimerization reaction proceeded in 1.5 hours to give **15** in 79% yield. 4-Bromoacetophenone (**16**) in the presence of $MeSO_3H$ also underwent the cyclotrimerization reaction in 1.5 hrs to give triphenylbenzene **17** in 85%, scheme 3. It is not obvious to what the reduction in the rate of the cylotrimerization of haloacetophenones **14** and **16** when compared to the reaction of acetophenone **1** should be attributed.



12 (X = 2-Cl)
14 (X = 3-Br)
16 (X = 4-Br)

13 (98%)
15 (79%)
17 (85%)

Scheme 3. Cyclotrimerization of haloacetophenone **12**, **14** and **16.**

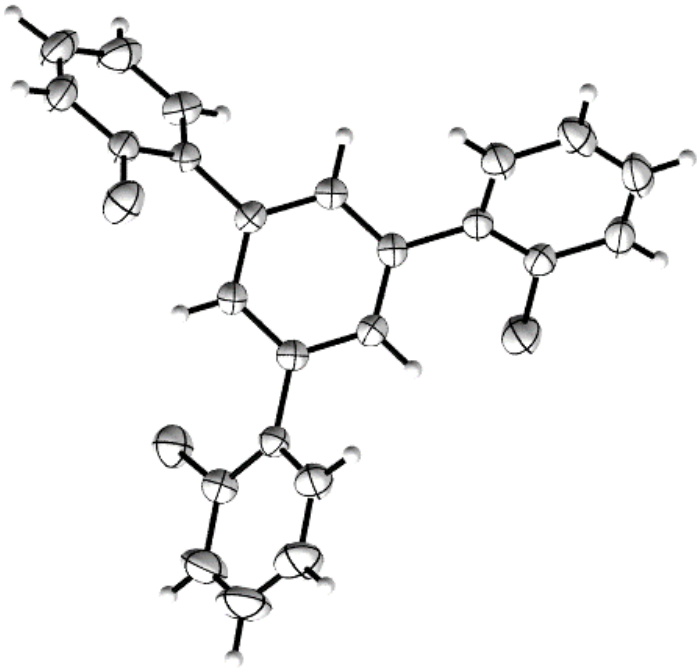
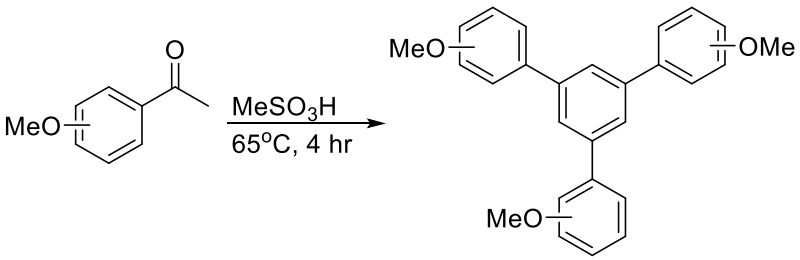


Figure 2. XRD crystal structure of **13.**

Electron-donating groups were expected to reduce the electrophilicity of the carbonyl carbon atom and consequently reduce the acidity of the α-hydrogens. The cyclotrimerization of acetophenones with electron-donating groups on the aromatic ring was expected to proceed at slower rate compared to that of acetophenone (**1**). Indeed, exposure of 2-methoxyacetophenone (**18**) to the reaction conditions described above led to a complex mixture of products in 4 hours. Gratifyingly, it was possible to isolate cyclotrimer **19** in 48% yield. In a similar fashion, 3,4-dimethoxyacetophenone (**20**) underwent the cyclotrimerization reaction also in 4 hours to give cyclotrimer **21** in 40% yield, scheme 4.



Scheme 4. Cyclotrimerization of methoxyacetophenones **18** and **20.**

Conclusions

In summary, the cyclotrimerization of various acetophenones to 1,3,5-triphenylacetophenones were promoted under mild reaction conditions by using $MeSO_3H$ as a catalyst without an organic solvent. These conditions afforded 1,3,5-triphenylbenzenes in low yields when the substrates were acetophenones with

methoxy substituents on the aromatic ring and high yields for acetophenone substrates with halogen substituents. All the substituted acetophenones underwent the cyclotrimerization at rates slower than that of acetophenone. The XRD crystal structure of **13** is described for the first time in literature.

Experimental Section

General. Column chromatography was done on columns packed with Merck silica gel 60-80 mesh with particle size 0.0400-0.0630 nm. The X-ray crystal diffraction data was collected using Bruker D8 Quest diffractometer (Bruker, Madison, WI, USA) equipped with a Mo monochromator (λ = 0.71076 Å). The X-ray crystallographic data for compounds **2** and **13** were deposited at the Cambridge Crystallographic Data Center with CCDC reference numbers 2299249 and 2296414 respectively.

Typical procedure. Acetophenone (1.47 g, 0.0122 mol) was treated with methanesulfonic acid (1.0 ml, 0.0122mol) and heated at 65℃ until acetophenone could not be detected by TLC (30 minutes). Thereafter, the reaction mixture was quenched with sodium hydrogen carbonate and extracted three times with chloroform. The organic layers were mixed, dried with $MgSO_4$ and concentrated under pressure. The crude product was purified using silica gel column chromatography and eluting with hexane.

Physiochemical and spectral data of the synthesized compounds

1,3,5-Triphenylbenzene (2).[8] White crystals; mp 173-175 ℃ (lit. 172-173 ℃).[8] ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 7.31 (3H, dd, *J* 7.4 Hz, H-4', 4'' and 4'''), 7.41 (6H, dd, *J* 7.6 Hz, H-3', 3'', 3''', 5', 5'' and 5'''), 7.75 (6H, d, *J* 7.7 Hz, H-2', 2'',2''', 6', 6'' and 6'''), 7.80 (3H, s, H-2, 4 and 6); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 123.6 (C-2, 4 and 6), 126.2 (C-2', 2'', 2''', 6', 6'' and 6'''), 126.5 (C-4', 4'' and 4''), 127.8 (C-3', 3'', 3''', 5', 5'', and 5''), 139.8 (C-1, 3 and 5) 141.3 (C-1', 1'' and 1'''). GC/MS (EI) *m/z* 306 $[M]^+$

1,3,5-Tris-(2-chlorophenyl) benzene (13).[9] Yellow crystals; mp 160-162 ℃ (lit. 164-166 ℃).[9] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.30 (6H, m, H-4', 4'', 4''', 5', 5'' and 5'''), 7.50 – 7.47 (3H, m, H-3', 3'' and 3'''), 7.51 (3H, d, *J* .7.7 Hz, H-6', 6'' and 6'''), 7.61 (3H, s, H-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 127.0 (C-2, 4 and 6), 128.8 (C-5', 5'' and 5'''), 129.9 (C-6', 6'' and 6'''), 130.1 (C-3', 3'', 3''', 4', 4'' and 4'''), 132.6 (C-2', 2'' and 2'''), 138.9 (C-1, 3, 5), 139.9 (C-1', 1'' and 1''') GC/MS (EI) *m/z* 408 $[M]^+$

1,3,5-Tris-(3-bromophenyl) benzene (15).[10] Light yellow crystals; mp 166-168 ℃ (lit. 170-174 ℃).[10] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (3H, dd, *J* 7.9 Hz, H-5', 5'' and 5'''), 7.54 (3H, ddd, *J* 8.0, 2.1, 1.1 Hz, H-6', 6'' and 6'''), 7.60 (3H, dt, *J* 7.8, 1.3 Hz, H-4', 4'' and 4'''), 7.71 (3H, s, H-2', 2'' and 2'''), 7.82 (3H, s, H-2, 4, 6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 123.2 (C-3', 3'' and 3'''), 125.7 (C-2, 4, 6), 126.1 (C-4', 4'', 4''', 6', 6'' and 6'''), 130.6 (C-5', 5'' and 5'''), 130.9 (C-2', 2'' and 2'''), 141.3 (C-1, 3, 5), 142.8 (C-1', 1'' and 1'''). GC/MS (EI) *m/z* 542 $[M]^+$

1,3,5-Tris-(4-bromophenyl) benzene (17).[8,10] Dark yellow crystals; mp 259-262 ℃ (lit. 262-264 ℃).[8] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (6H, m, H-2', 2'', 2''', 6', 6'' and 6'''), 7.61 (6H, m, H-3', 3'', 3''', 5', 5'' and 5'''), 7.69 (3H, s, H-2, 4, 6). ^{13}C NMR (100 MHz, $CDCl_3$) δ 122.1 (C-4', 4'' and 4'''), 125.0 (C-2, 4, 6), 128.9 (C-3', 3'', 3''', 5', 5'' and 5'''), 132.0 (C-2', 2'', 2''', 6', 6'' and 6'''), 139.6 (C-1, 3 and 5), 141.5 (C-1', 1'' and 1'''). GC/MS (EI) *m/z* 542 $[M]^+$

1,3,5-Tris-(2-methoxyphenyl) benzene (19).[8] Brown powder; mp 140-146 ℃ (lit. 143-146 ℃).[8] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (9H, s, 3 x OCH_3), 7.05 (3H, d, *J* 8.0 Hz, H-3', 3'' and 3'''), 7.10 (3H, t, *J* 8.0 Hz, H-5', 5'' and 5'''), 7.38 (3H, t, *J* 8.0 Hz, H-4', 4'' and 4'''), 7.50 (dd, *J* 8.0 and 1.8 Hz, H-6', 6'' and 6'''), 7.76 (3H, s, H-2, 4 and 6). ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.7 (3 x -OCH_3), 111.3 (C-3', 3'' and 3'''), 120.8 (C-5', 5'' and 5'''), 128.5 (C-2,

4 and 6), 129.7 (C-4', 4'' and 4'''), 131.0 (C-6', 6'' and 6'''), 131.2 (C-1', 1'' and 1'''), 137.8 (C-1, 3 and 5), 156.8 (C-2', 2'' and 2'''). GC/MS (EI) *m/z* 396 $[M]^+$

1,3,5-Tris-(3,4-dimethoxyphenyl) benzene (21).[11] Brown powder; mp 171.2-171.6℃ (lit 171.4-172.9 ℃).[11] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98 (9H, s, 3 x 4-OC<u>H</u>$_3$), 3.99 (9H, s, 3-OC<u>H</u>$_3$), 7.02 (3H, d, *J* 8.3 Hz, H-5', 5'' and 5'''), 7.21 (3H, s, H-2', 2'' and 2'''), 7.29 (3H, d, *J* 8.3 Hz, H-6', 6'' and 6'''), 7.68 (3H, s, H-2, 4 and 6). ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.5 (6 x O<u>C</u>H$_3$), 111.1 (C-5', 5'' and 5'''), 111.9 (C-2', 2'' and 2''), 120.1 (C-6', 6'' and 6'''), 124.9 (C-2, 4 and 6), 134.7 (C-1, 3 and 5), 142.7 (C-1', 1'' and 1'''), 149.3 (C-4', 4'' and 4'''), 149.7 (C-3', 3''and 3'''). GC/MS (EI) *m/z* 486 $[M]^+$.

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Supplementary Material

NMR spectra and XRD data of the prepared 1,3,5-phenylbenzenes can be found online in the supplementary material.

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