Pergamon

Tetrahedron Letters 41 (2000) 6545–6549

TETRAHEDRON LETTERS

Synthesis of linked 1,3,5-triaroylbenzenes via enamine-directed alkyne cyclotrimerization

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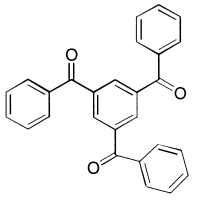
Received 8 June 2000; accepted 4 July 2000

Abstract

Triaroylbenzenes connected via *m*-xylyl, *p*-xylyl, 4,4′-biphenyl, and 1,3,5-benzenetriyl linking units have been prepared in good yield by condensation of bis(enaminones) with aryl ethynyl ketones. The required bis(enaminones) were conveniently prepared starting from the corresponding bis- or tris(halomethyl) linking units and 3-hydroxybenzaldehyde.

Keywords: alkynes; cyclotrimerization; enamines; arenes.

The design and synthesis of molecular hosts capable of operating in solution and/or the solid-phase continues to attract the attention of an increasingly interdisciplinary cross-section of the chemical community. Synthetic solution phase receptors have provided valuable insight into the factors responsible for molecular recognition events occurring in biological systems.[1] In addition, such receptors have great potential for use in the development of new catalysts, sensors, and sequestering agents.[2] Solid-phase host–guest complexes provide a means to study weak intermolecular interactions (such as C–H···O hydrogen bonding)[3] and also may have applications in areas such as non-linear optics[4] and separations technology.[5]



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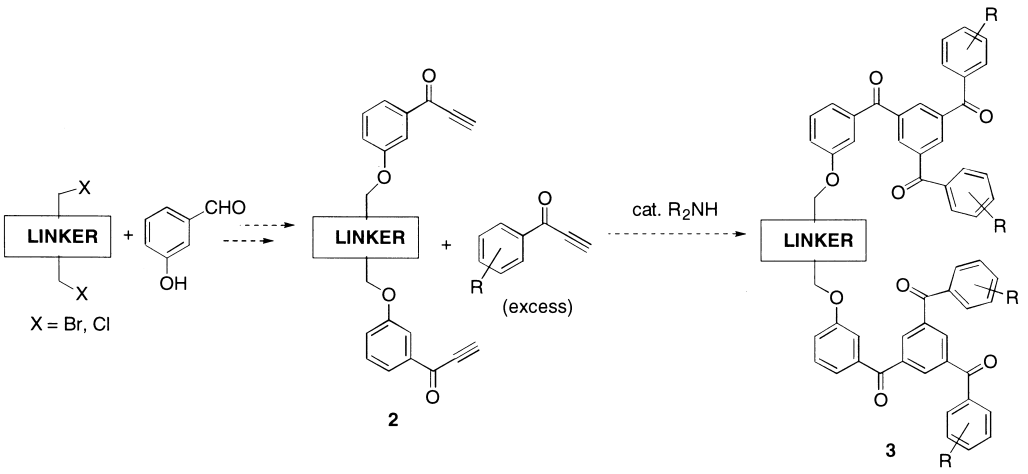
0040-4039/00/$ - see front matter
PII: S0040-4039(00)01125-4

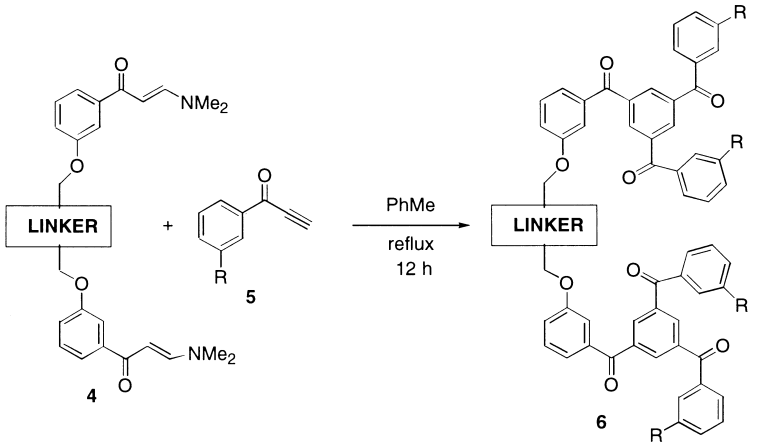
In connection with a study aimed at developing new molecular receptors capable of participating in supramolecular assemblies, we have begun exploring the suitability of 1,3,5-triaroylbenzene derivatives (possessing the general structure illustrated for the parent compound **1**) as a central architectural motif. Simple 1,3,5-triaroylbenzenes are easily prepared using a method first reported by Balasubramanian that entails amine-catalyzed cyclotrimerization of aryl ethynyl ketones.[6] Reports from this laboratory have described the ability of methoxy- and nitro-substituted derivatives to serve as solid-state inclusion hosts for various small molecule guests.[7] Given these preliminary findings, it was deemed worthwhile to investigate the feasibility of constructing more elaborate 'linked' triaroylbenzenes with the aim of using these materials as precursors for new molecular receptor frameworks.

The synthetic route envisioned for the preparation of the target structures is illustrated in Scheme 1. Attachment of 3-hydroxybenzaldehyde moieties to appropriately functionalized 'spacer' units (e.g. *m*-xylyl) followed by conversion of the aldehyde residues to aryl ethynyl ketones should give **2**. Cross-trimerization of **2** with a second aryl ethynyl ketone reactant should then afford the desired 'linked' triaroylbenzenes **3**. The success of this route is predicated upon the ability to perform cross-cyclotrimerizations leading to unsymmetrically substituted 1,3,5-triaroylbenzene derivatives. Iwamura has reported a successful cross-trimerization between two different aryl ethynyl ketones in the presence of a catalytic amount of diethylamine.[8] The desired triaroylbenzene, however, was isolated in 31% yield after separation from a statistical mixture of other symmetrical and unsymmetrical cyclotrimers. Application of this method for the trimerization of **2** (linker = *m*-xylyl)[9,10] and the aryl ethynyl ketone derived from *m*-anisaldehyde did indeed provide the desired linked bis(triaroylbenzene); unfortunately, the isolated yield of 20% and the extensive chromatography required to obtain homogeneous material rendered this approach unacceptable.



Scheme 1.

Consequently, an alternative means of effecting the desired cross-cyclotrimerization was required. Mechanistic studies of the cyclotimerization reaction, also reported by Iwamura,

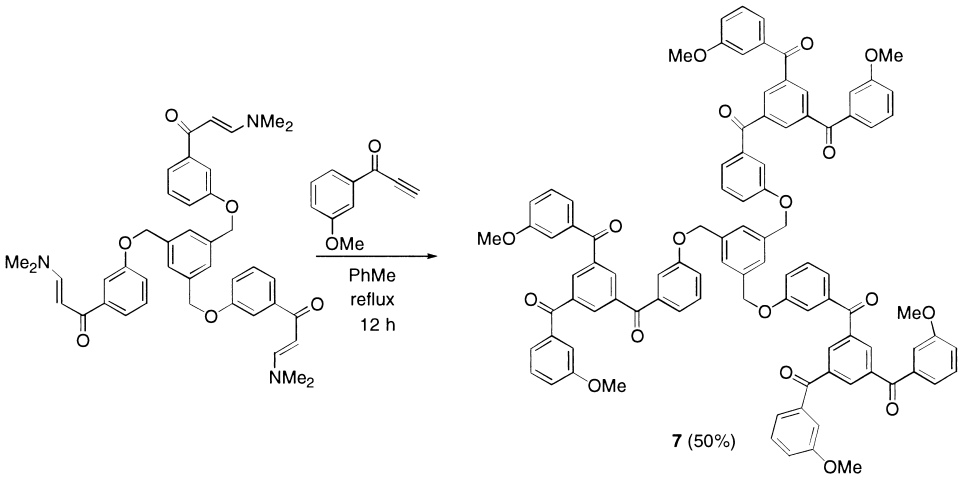


Entry	Linker	R	Yield (%)
1	*p*-C_6H_4	OMe	66
2	*p*-C_6H_4	NO_2	48
3	*m*-C_6H_4	OMe	56
4	*m*-C_6H_4	NO_2	47
5	4,4'-biphenyl	OMe	60
6	4,4'-biphenyl	NO_2	43

Scheme 2.

strongly suggest that the amine catalyst initially reacts with an alkynyl moiety to form an enamine.[11] Sequential condensation of this enamine with two additional molecules of aryl ethynyl ketone result in formation of a cyclic diene from which the amine is eliminated, thereby generating a new arene ring. Other experiments established that the initially formed enamine is not in equilibrium with the free amine and aryl ethynyl ketone. Thus, if the alkyne residues in **2** were first converted to the corresponding enaminones prior to condensation with the second aryl ethynyl ketone reaction partner, unwanted oligomerization of **2** should be suppressed and enamine-directed cross-cyclotimerization should be favored.

To test this theory, bis(ethynyl ketones) exhibiting the general structure depicted in **2** were transformed to the corresponding *N*,*N*-dimethyl enaminones (**4**) by treatment with $Me_2NH{\cdot}HCl$ in the presence of K_2CO_3 (Scheme 2). Gratifyingly, heating a mixture of **4** and an excess of an aryl ethynyl ketone **5** (~8 equiv.) in toluene resulted in smooth trimerization to afford the desired linked 1,3,5-triaroylbenzenes (**6**) in good isolated yields,[10] especially given the fact that six new C–C bonds are formed during the course of the reaction. In addition, isolation of **6** from the crude reaction mixture was accomplished by application of routine chromatographic techniques as the only tractable by-product generated was the symmetrical cyclotrimer of **5**.[12] Both electron rich (R = OMe) and electron deficient ($R = NO_2$) aryl ethynyl ketones proved to be suitable reactants, although nitro-substituted linked triaroylbenzenes were isolated in slightly lower yields. The nature of the linker moiety connecting the 1,3,5-triaroylbenzene frameworks could be varied as well. This protocol was also suitable for the preparation of tris(triaroylbenzene) derivative **7** in which the individual cyclotrimers are connected via a 1,3,5-trisubstituted phenyl ring (Eq. (1)).[10,13]



(1)

In summary, an efficient and modular synthetic route for the preparation of linked bis- and tris(1,3,5-triaroylbenzenes) has been established in which an enamine-directed alkyne cross-cyclotimerization is the key transformation. The ability of these linked triaroylbenzenes to function as novel solid-state inclusion hosts is currently under investigation. Additionally, further synthetic elaboration of the triaroylbenzene framework to ultimately deliver new cyclophanes and cage compounds is being examined.

Acknowledgements

Financial support for this work was provided by the University of Missouri–St. Louis Department of Chemistry. Support for departmental NMR facilities was provided by the NSF (CHE-9318696).

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13. The precursor to **7** was prepared using the route described in Ref. 9 starting from 1,3,5-tris(bromomethyl)benzene: Cochrane, W. P.; Pauson, P. L.; Stevens, T. S. *J. Chem. Soc. C* **1968**, 630.