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Reports

Microwave-Assisted Solid-Supported Alkyne Cyclotrimerization Reactions for Combinatorial Chemistry

Douglas D. Young, Lakshminath Sripada, and Alexander Deiters*

Department of Chemistry, North Carolina State University, Raleigh, North Carolina 27695-8204

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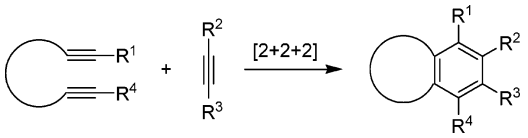
The formation of functionalized benzene rings via [2+2+2] cyclotrimerization reactions of a diyne and a mono-alkyne enables a highly convergent synthesis of cyclic structures (Scheme 1), especially when compared to other approaches of generating substituted aromatic ring systems, e.g., Friedel−Crafts reactions or directed lithiations.[1] The versatility of the cyclotrimerization approach has inspired the development of several specialized catalyst systems[2,3] and led to numerous successful applications in total synthesis.[4] Although biologically important structures can be accessed and hundreds of diverse alkyne building blocks are commercially available, or can be efficiently synthesized, only very limited examples of [2+2+2] cyclotrimerization reactions applied to combinatorial chemistry exist.[5] We hypothesize that this is due to several persisting problems of this technology, including chemoselectivity, regioselectivity, and reactivity issues. The former leads to side products formed by di- and trimerization of diyne starting materials (especially in the case of less reactive mono-alkynes[3,6]), and the latter prevents the facile construction of highly substituted aromatic rings or benzenes fused to a simple six-membered ring system.[1]

By conducting [2+2+2] cyclotrimerization reactions on a solid support, we were able to spatially separate the alkyne precursors and thus provide a solution to the chemoselectivity problem.[7,8] Here, we are reporting a solution to the reactivity problem by employing microwave irradition[9] to facilitate the formation of otherwise inaccessible ring structures and to greatly reduce the reaction times of solid-supported cyclotrimerizations from days to minutes. Moreover, by using microwave irradiation, we can react substrates which previously eluded cyclotrimerization. These developments lead to unifying conditions for cyclotrimerization reactions of a broad range of alkynes and provide excellent reaction conditions for the assembly of combinatorial libraries with an aromatic core structure. While this initial study was not conducted in a parallel fashion, this methodology can easily be automated to produce libraries of hundreds of compounds in only a few days using commercially available automated microwave synthesizers.

Scheme 1. General Cyclotrimerization Reaction of a Diyne and a Mono-alkyne Yielding a Fused Benzene.



The five diyne substrates **1**−**5** (Figure 1) used in this study have been prepared according to literature conditions,[10] and the mono-alkyne reaction partners were either synthesized (**6**)[11] or purchased (**7**−**12**, Sigma-Aldrich). Together, these substrates allow for the probing of the functional group compatibility of the microwave-assisted [2+2+2] cyclotrimerization reaction. The reaction is compatible with a variety of functionalities, inculding alkoxy groups (in **6**), alkyl chains (in **7** and in **12**), aromatic rings (in **6**, **10**, and **11**), chlorine atoms (in **8**), cyano groups (in **9**), and pyridyl groups (in **11**). To investigate the reactivity enhancing effects through microwave irradiation, we were especially interested in employing the otherwise difficult to react diynes **3**−**5** and the less reactive internal alkyne **12**.

For initial investigations, we immobilized the precursor **1** on a standard polystyrene resin (100−200 mesh, 2% crosslinking) using a trityl linker (0.6 mmol/g, Scheme 2).[12]

* Corresponding author. E-mail: alex_deiters@ncsu.edu.

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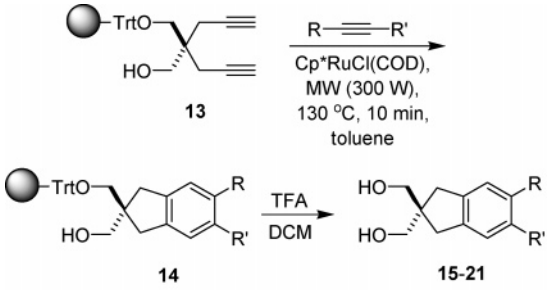
Scheme 2. Microwave-Assisted [2+2+2] Cyclotrimerization Reactions toward Indanes.



Cmpd	R	R'	Yield
15	Bu	H	86%
16	$(CH_2)_3Cl$	H	88%
17	$(CH_2)_3CN$	H	83%
18	CH_2OBn	H	85%
19	Ph	H	75%
20	Pyr	H	78%
21	Et	Et	75%

The immobilized substrate **13** has previously been cyclotrimerized by us using Wilkinson's catalyst under thermal conditions (10 mol % $Rh(Ph_3P)_3Cl$, DCM, 60 °C) requiring an extended reaction time of 48 h. However, when we conducted [2+2+2] cyclotrimerization reactions using the Cp*RuCl(COD) catalyst[3] (10 mol %) under microwave irradiation in a CEM Discover synthesizer (300 W, 130 °C, toluene), we observe rapid transformation of **13** into **14** (within 10 min) and obtained the indanes **15**−**21** in excellent yield (75−88%) and high purity (>90%). The shortened reaction time and the higher yields represent a substantial enhancement of the solid-supported [2+2+2] cyclotrimerization reaction and provide an excellent tool for the rapid assembly of small molecule arrays based on fused benzenes. Moreover, it was not necessary to degas the solvent as in the case of previous reactions, eventually facilitating the application of this methodology in automated synthesis. As in previous cases, spatial separation on the solid-support completely prevented formation of diyne dimers and trimers, as observed in solution-phase reactions (especially with less reactive internal alkynes, R and R′ ≠ H).[3,6]

To investigate the facile synthesis of isoindolines and, more importantly, tetrahydroisoquinolines, we immobilized the diynes **2** and **3** on a polystyrene resin as **22** and **31** (0.71 and 0.58 mmol/g, respectively) via a trityl linker. As expected, microwave-mediated cyclotrimerization reactions of **22** to **23** proceeded rapidly and almost quantitatively (Scheme 3). The isoindolines **24**−**30** were isolated in 87−96% yield and with >90% purity, after just a 10 min cyclotrimerization reaction—representing a substantial improvement over previous reaction conditions.[8,13]

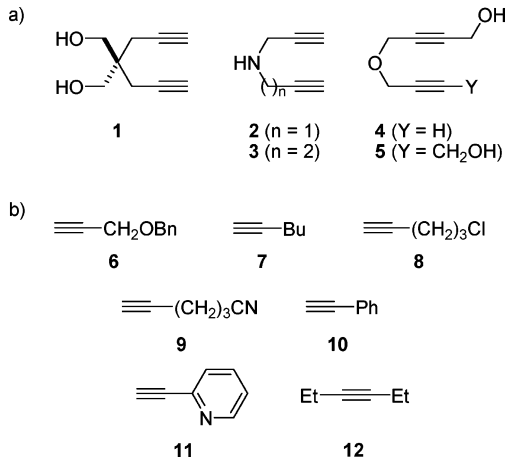
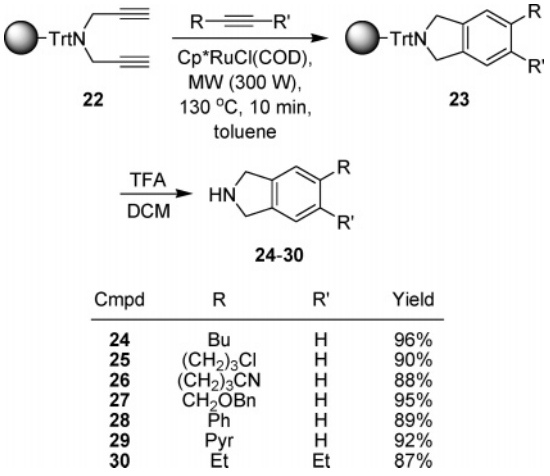


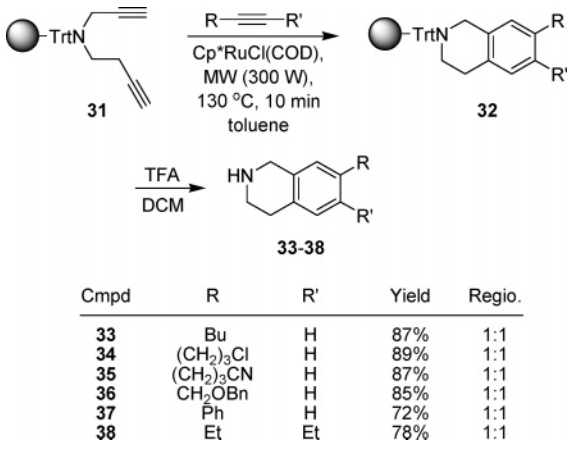
Figure 1. Diynes **1**−**5** and mono-alkynes **6**−**12** used in this study.

Scheme 3. Microwave-Assisted [2+2+2] Cyclotrimerization Reactions toward Isoindolines.



Cmpd	R	R'	Yield
24	Bu	H	96%
25	$(CH_2)_3Cl$	H	90%
26	$(CH_2)_3CN$	H	88%
27	CH_2OBn	H	95%
28	Ph	H	89%
29	Pyr	H	92%
30	Et	Et	87%

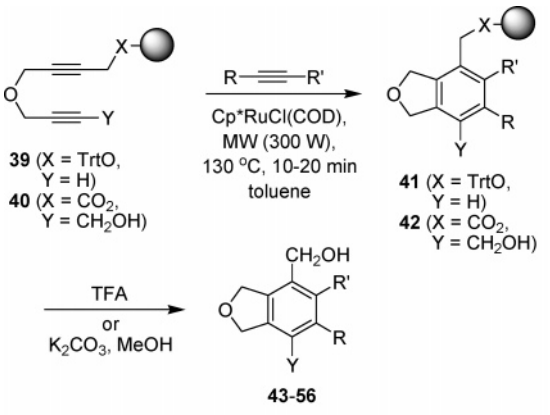
Scheme 4. Microwave-Assisted [2+2+2] Cyclotrimerization Reactions toward Tetrahydroisoquinolines.



Cmpd	R	R'	Yield	Regio.
33	Bu	H	87%	1:1
34	$(CH_2)_3Cl$	H	89%	1:1
35	$(CH_2)_3CN$	H	87%	1:1
36	CH_2OBn	H	85%	1:1
37	Ph	H	72%	1:1
38	Et	Et	78%	1:1

Although isoindolines are important pharmacophores found in molecules with a wide range of biological activities, especially antibacterial activity,[14] we were most interested in assembling the homologous tetrahydroisoquinoline skeleton due to its abundance in nature. Gratifyingly, the microwave-mediated cyclotrimerization of **31** smoothly proceeded to the immobilized tetrahydroisoquinoline **32** (Scheme 4), and after cleavage from the resin, the compounds **33**−**38** were obtained in good yields (72−89%) as a 1:1 mixture of regioisomers. Thus, we achieved the facile construction of this important core structure which is found in a wide range of biologically important natural products (for example, in protoberine alkaloids, ipecacuanha alkaloids, and benzyltetrahydroisoquinoline alkaloids).[15] The transformation **31** to **32** showcases the enhancing effects of microwave irradiation in conjunction with a solid-support on the Ru-catalyzed [2+2+2] cyclotrimerization reaction. When the same transformation was carried out in the solution

Scheme 5. Microwave-Assisted [2+2+2] Cyclotrimerization Reactions toward Phthalans.



Cmpd	X	Y	R	R'	Yield	Regio.
43	TrtO	H	Bu	H	86%	9:1
44	TrtO	H	$(CH_2)_3Cl$	H	91%	9:1
45	TrtO	H	$(CH_2)_3CN$	H	83%	9:1
46	TrtO	H	CH_2OBn	H	82%	9:1
47	TrtO	H	Ph	H	88%	9:1
48	TrtO	H	Pyr	H	87%	9:1
49	TrtO	H	Et	Et	79%	--
50	CO_2	CH_2OH	Bu	H	72%	--
51	CO_2	CH_2OH	$(CH_2)_3Cl$	H	85%	--
52	CO_2	CH_2OH	$(CH_2)_3CN$	H	88%	--
53	CO_2	CH_2OH	CH_2OBn	H	75%	--
54	CO_2	CH_2OH	Ph	H	78%	--
55	CO_2	CH_2OH	Pyr	H	62%	--
56	CO_2	CH_2OH	Et	Et	56%	--

phase, complex compound mixtures were obtained and the product was only isolated in diminished yield (data not shown).

To further investigate the generality of the microwave-assisted, solid-supported cyclotrimerization reaction, the diynes **4**−**5** were synthesized and immobilized as **39**−**40** (0.56 and 0.45 mmol/g, respectively). The precursor **39** was selected to investigate the effects of microwave irradiation on the regioselectivity of the cyclotrimerization reaction. Previous solid-phase cyclotrimerizations with **39** required a sterically less demanding carboxy linkage for immobilization on the polymeric support;[8] in contrast, microwave irradiation enables the application of a bulky, but readily cleavable, trityl linker. The reactions of **39** with the alkynes **6**−**12** toward **41** proceeded smoothly (Scheme 5), delivering up to pentasubstituted benzenes **43**−**49** in good yields (82−91%) and high purity (>90%). Gratifyingly, with the terminal alkynes **6**−**11**, high regioselectivity (9:1) leading to the meta isomer **41** (R′ = H) was observed. These experiments demonstrate that the reactivity enhancing effects of microwave irradiation do not lead to lower regioselectivities. In order to investigate the extent of the reactivity enhancement, we immobilized the diyne **5** as **40**, bearing two internal triple bonds. Interestingly, we had to employ the less sterically demanding carboxy linker to maintain reactivity in this case, emphasizing the importance of a careful linker selection in solid-supported chemistry.[12] As expected, the products **50**−**56** were obtained in slightly lower yields (56−88%), due to two less reactive, internal triple bonds in the precursor **40**. The reaction time needed to be increased from 10 to 20 min to achieve full conversion; however, this reaction was especially inefficient under thermal conditions (<10% conversion, data not shown). Additionally, a hexasubstituted benzene **56** could be obtained, which was previously not possible under conventional thermal reaction conditions (data not shown).

In summary, we demonstrated the reactivity enhancing effects of microwave irradiation combined with the effects of spatial diyne separation on a polymeric support on the ruthenium-catalyzed [2+2+2] cyclotrimerization reaction. The conducted transformations were highly efficient and a high level of chemoselectivity was observed. Moreover, microwave-irradiation did not affect the regioselectivity of the cyclotrimerization reaction when differentially substituted diyne precursors were used. The developed methodology provides rapid access to a variety of carbo- and heterocyclic structures from simple starting materials. Moreover, it can be directly employed in the synthesis of small molecule arrays of pharmacologically relevant structures (e.g., isoindolines and tetrahydroisoquinolines), due to excellent product yields, extremely short reaction times (minute time scale), and simple reaction conditions (no solvent degassing necessary). We believe that the demonstrated approach of using microwave irradiation in conjunction with a solid support can also find application in the optimization and realization of other transition metal-catalyzed cycloaddition reactions for combinatorial chemistry.

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Supporting Information Available. General cyclotrimerization protocol, ^{1}H NMR data of compounds **20**, **29**, **34**−**36**, **38**, **48**, and **50**−**56**. This information is available free of charge via the Internet at http://pubs.acs.org.

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