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Microwave-Assisted Intramolecular [2 + 2] Allenic Cycloaddition Reaction for the Rapid Assembly of Bicyclo[4.2.0]octa-1,6-dienes and Bicyclo[5.2.0]nona-1,7-dienes

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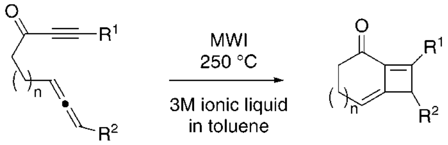
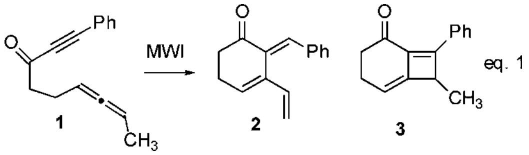
ABSTRACT



Microwave irradiation of alkynyl allenes affords an intramolecular [2 + 2] cycloaddition reaction. This cycloaddition provides an efficient route to bicyclomethylenecyclobutenes. The reaction occurs with complete regioselectivity for the distal double bond of the allene for the selective formation of a variety of hetero- and carbocyclic substrates. Bicyclo[4.2.0]octadienes and bicyclo[5.2.0]nonadienes have been prepared in high yield.

Since the pioneering work of Gedye[1] and Giguere/Majetich[2] in 1986, microwave irradiation (MWI) has frequently been employed as a thermal source for many organic reactions. Advantages to MWI include minimization of thermal decomposition of reagents and products by eliminating potential temperature gradients and localized overheating, which are common to conventional heating methods. In addition, MWI also greatly accelerates reaction rates and typically provides better yields with fewer byproducts.[3] During our studies on the scope and limitations of the formal Rh(I)-catalyzed allenic Alder-ene reaction, we turned to thermal conditions to test whether the Rh(I) catalyst is indeed necessary for the cycloisomerization process. Interestingly, exposure of alkynyl allene **1** to MWI did produce a 10% yield of the formal Alder-ene product, triene **2**. More surprisingly though was the formation of the [2 + 2] cycloadduct **3** as the major product in 66% yield (eq 1).



[2 + 2] Cycloaddition reactions between an allene and an *alkene* are well documented and constitute a powerful method for the synthesis of methylenecyclobutane derivatives via photochemical initiation and Lewis acid and transition metal promotion.[4] On the other hand, only scattered reports have appeared on [2 + 2] cycloaddition reactions between an *alkyne* and an allene. Cook observed a [2 + 2] cycloadduct as a byproduct during a molybdenum-mediated intramolecular allenic Pauson−Khand reaction.[5] Similarly, Hammond has reported a molybdenum-catalyzed intramolecular [2 + 2] cycloaddition for the preparation of bicyclo- and heterobicyclo-*gem*-difluorocyclobutenes.[6] Finally, Tamura

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[1] Gedye, R.; Smith, F.; Westaway, K.; Ali, H.; Baldisera, L.; Laberge, L Rousell, J. *Tetrahedron Lett.* **1986**, *27*, 279.

[2] Giguere, R. J.; Bray, T. L.; Duncan, S. M.; Majetich, G. *Tetrahedron Lett.* **1986**, *27*, 4945.

[3] For reviews, see: Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250. Varma, R. S. *Pure Appl. Chem.* **2001**, *73*, 193. Nuchter, M.; Ondruschka, B.; Bonrath, W.; Gum, A. *Green Chem.* **2004**, *6*, 128.

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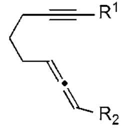
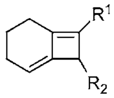
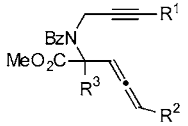
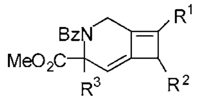
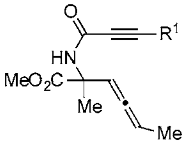
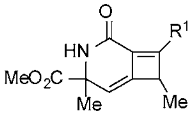
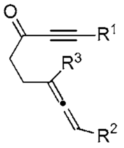
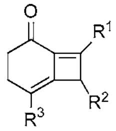
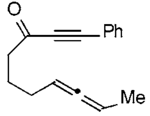
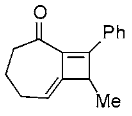
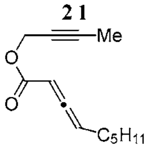
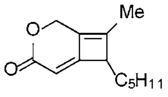
has demonstrated an intermolecular [2 + 2] cycloaddition reaction between an alkyne and an allene. The scope of the latter reaction appears somewhat limited since only two examples were reported.[7]

This novel microwave-assisted reaction and the potential synthetic utility of the structurally distinct products inspired us to investigate the scope and limitations of this rare [2 + 2] cycloaddition reaction. The results obtained to date are reported herein. We began our investigations by screening a variety of conditions to find the optimal procedure for the [2 + 2] cycloaddition. For these studies, it seemed most advantageous to perform the reaction on substrates that are not capable of undergoing an allenic Alder-ene reaction. Initially, allenyne **4** (entry 1) was heated to 110 °C in toluene for 15 min. These conditions afforded only starting materials on the basis of the ^{1}H NMR spectrum of the concentrated reaction. Therefore, it was decided that higher temperatures were needed to effect this cycloaddition reaction. Higher temperatures (>200 °C) were obtained by doping the toluene with an ionic liquid, 1-ethyl-3-methylimidazolium hexafluorophosphate.[8] Heating compound **4** to 220 °C for 15 min showed mostly the [2 + 2] cycloadduct **23** with only a small amount of starting material. This reaction was repeated at 250 °C for 15 min, at which time only cycloadduct **23** was obtained in 74% yield after purification via column chromatography. This same reaction was repeated at 280 °C for 15 min, but the higher temperature gave a dark brown solution and a black gel at the bottom of the reaction vial. The ^{1}H NMR spectrum of the crude material showed that the starting material had decomposed. On the basis of these experiments, the ideal conditions for performing these allenic [2 + 2] cycloaddition reactions are a 3 M solution of 1-ethyl-3-methylimidazolium hexafluorophosphate in toluene at 250 °C (MWI) for 15 min. Next, the scope of this reaction was investigated by subjecting alkynyl allenes possessing a wide range of substituents and functionality to the optimized formal cycloaddition reaction conditions. Allenyne **5**, also possessing a phenyl group on the terminus of the alkyne but an additional methyl group on the allene, gave cyclobutene

Table 1. Formation of Bicycloalkadienes[a]

	Allenyne	Product	Yield
			
1	R^1 = Ph, R^2 = H, **4**	**23**	74%
2	R^1 = Ph, R^2 = Me, **5**	**24**	63%[b]
3	R^1 = TMS, R^2 = Me, **6**	**25**	S.M.
4	R^1 = C_4H_9, R^2 = H, **7**	**26**	S.M.
			
5	R^1 = Ph, R^2 = Me, R^3 = Bn, **8**	**27**	60%
6	R^1 = Me, R^2 = H, R^3 = Me, **9**	**28**	81%
7	R^1 = H, R^2 = H, R^3 = Me, **10**	**29**	Dec
8	R^1 = Me, R^2 = Me, R^3 = Me, **11**	**30**	triene 54%
			
9	R^1 = Ph, **12**	**31**	60%
10	R^1 = Me, **13**	**32**	21%[c]
			
11	R^1 = Ph, R^2 = Me, R^3 = Me, **14**	**33**	79%
12	R^1 = *p*-OMe-Ar, R^2 = R^3 = Me, **15**	**34**	70%
13	R^1 = 1-cyclohexene, R^2 = H, R^3 = H, **16**	**35**	77%
14	R^1 = Ph, R^2 = H, R^3 = H, **17**	**36**	68%
15	R^1 = Ph, R^2 = Me, R^3 = H, **18**	**37**	66%[d]
16	R^1 = TMS, R^2 = R^3 = Me, **19**	**38**	Dec
17	R^1 = C_4H_9, R^2 = R^3 = H, **20**	**39**	33%[e]
18	 **21**	 **40**	83%[f]
19	 **22**	 **41**	47%[g]

[a] Conditions: toluene, ionic liquid (1-ethyl-3-methylimidazolium hexafluorophosphate), microwave irradiation at 250 °C for 15 min. [b] Isolated a 7% yield of the triene. [c] Isolated a 30% yield of the triene. [d] Isolated a 10% yield of the triene. [e] Recovered an equal amount of starting material. [f] Microwave irradiation at 280 °C for 15 min. [g] Isolated a 28% yield of the triene.

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(4) Padwa, A.; Meske, M.; Murphree, S.; Watterson, S. H.; Ni, Z. *J. Am. Chem. Soc*. **1995**, *117*, 7071. Padwa, A.; Lipka, H.; Watterson, S. H.; Murphree, S. S. *J. Org. Chem*. **2003**, *68*, 6238. Snider, B. B.; Ron, E. *J. Org. Chem*. **1986**, *51*, 3643. Aben, R. W. M.; Braverman, S.; Scheeren, H. W. *Eur. J. Org. Chem*. **2003**, 894. Skattebol, L.; Stenstrom, Y. *Tetrahedron Lett*. **1983**, *24*, 3021. Hansen, T. V.; Skattebol., L.; Stenstrom, Y. *Tetrahedron* **2003**, *59*, 3461. Dauben, W. G.; Rocco, V. P.; Shapiro, G. *J. Org. Chem*. **1985**, *50*, 3155. Narasaka, K.; Hayashi, Y.; Shimadzu, H.; Niihata, S. *J. Am. Chem. Soc*. **1992**, *114*, 8869. Hayakawa, K.; Aso, K.; Shiro, M.; Kanematsu, K. *J. Am. Chem. Soc*. **1989**, *111*, 5312. Yoshida, M.; Hidaka, Y.; Nawata, Y.; Rudzinski, J. M.; Osawa, E.; Kanematsu, K. *J. Am. Chem. Soc*. **1988**, *110*, 1232, 1238.

(5) Cao, H.; Flippen-Anderson, J.; Cook, J. M. *J. Am. Chem. Soc*. **2003**, *125*, 3230.

(6) Shen, Q.; Hammond, G. B. *J. Am. Chem. Soc*. **2002**, *124*, 6534.

(7) For an intermolecular [2 + 2] cycloaddition reaction, see: Kimura, M.; Horino, Y.; Wakamiya, Y.; Okajima, T.; Tamaru, Y. *J. Am. Chem. Soc*. **1997**, *119*, 10869. Horino, Y.; Kimura, M.; Tanaka, S.; Okajima, T.; Tamaru, Y. *Chem. Eur. J*. **2003**, *9*, 2419.

(8) This is an alternative to using rather expensive ionic liquids as the solvent. This technique of using an ionic liquid as a “doping agent” to increase the ability of the solution to absorb microwave energy was first introduced by Ley. See: Ley, S. V.; Leach, A. G.; Storer, R. I. *J. Chem. Soc*. **2001**, 358. Also, the solvent selection proved to be crucial to the success of these reactions. A variety of solvents commonly used for MWI were examined, and it was found that DMSO or DMF led to decomposition.

24 in a 63% yield (entry 2). Addition of a methyl group on the terminus of the allene did not appear to significantly affect the efficiency of this [2 + 2] cycloaddition process; however, a 7% yield of the triene was also observed. Substitution of the terminus of the alkyne with either a TMS (entry 3) or an alkyl group (C_4H_9, entry 4) gave only unreacted starting material under the standard reaction conditions. Attempts have not been made to optimize the reaction conditions for these substrates.

Next, in connection with the expansion of our diverging strategy for accessing libraries of small molecules possessing structurally unique scaffolds from a pivotal substrate, the [2 + 2] cycloaddition of amino acid containing allenynes was investigated.[9] Placement of a phenyl group on the terminus of the alkyne (R^1 = Ph, entry 5) gave a 60% yield of the [2 + 2] cycloadduct **27** (entry 5). For this series of substrates, an alkyl group on the terminus of the alkyne was tolerated as evidenced by enyne **9** (R^1 = Me) affording an 81% yield of compound **28**. Reaction of an allenyne **10** possessing terminal alkyne gave only decomposition (entry 7). Alternatively, addition of methyl group to the terminus of the allene and alkyne gave only the triene in 54% yield and none of the [2 + 2] cycloadduct **30** (entry 8).

The phenyl propiolamide containing allene **12** afforded 60% yield of the cycloadduct **31** (entry 9). However, an alkyl propiolamide **13** gave a 21% yield of cycloadduct **32** combined with a 30% yield of the triene (entry 10). Next, cycloaddition of alkynone-containing allenes were attempted. Again the substituent on the terminus of alkynes appeared to be a controlling factor in the efficiency of these reactions, with the phenyl group giving the highest conversions (compare entries 11, 12, 14, and 15 to 16 and 17). An olefin on the terminus of the alkyne was also tolerated and afforded good yields of cycloadduct **35** (entry 13). Interestingly, increasing the tether length by one methylene unit afforded the bicyclo[5.2.0]nona-1,7-diene **40** in 83% yield (entry 18). This is a rare example of forming a medium-sized ring using a [2 + 2] cycloaddition reaction. Finally, the allenic ester **22** gave a 47% yield of the bicyclic lactone **41** and a 28% yield of the triene.

In summary, we have discovered a microwave-assisted [2 + 2] cycloaddition reaction of an alkynyl allene that provides bicyclomethylenecyclobutenes in good to excellent yield. Details concerning the mechanism of the thermal [2 + 2] cycloaddition reaction of allenes remain unclear even though it has been extensively studied.[10] Convincing arguments for both a stepwise biradical mechanism and a concerted mechanism based upon frontier molecular orbital theory have been made. The substrates described within this manuscript are different from those previously reported and may assist in shedding light on this much-debated topic. We are continuing our studies into the scope and limitations of this new method and also investigating the synthetic utility of the cycloadducts. These results will be reported in due course.

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Supporting Information Available: Data and experimental procedures for all unknown compounds in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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[9] Brummond, K. M.; Mitasev, B. *Org. Lett.* **2004**, *6*, 2245.

[10] Pasto, D. J. J. *Am. Chem. Soc.* **1979**, *101*, 37. Dolbier, W. R.; Weaver, S. L. *J. Org. Chem.* **1990**, *55*, 711. Pasto, D. J.; Kong, W. *J. Org. Chem.* **1988**, *53*, 4807. Pasto, D. J.; Sugi, K. D.; Alonso, D. E. *J. Org. Chem.* **1992**, *57*, 1146.