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A New and Practical Five-Carbon Component for Metal-Catalyzed [5 + 2] Cycloadditions: Preparative Scale Syntheses of Substituted Cycloheptenones

Paul A. Wender,* Alaric J. Dyckman, Craig O. Husfeld, and Marc J. C. Scanio

Department of Chemistry, Stanford University, Stanford, California, 94305-5080
wenderp@leland.stanford.edu

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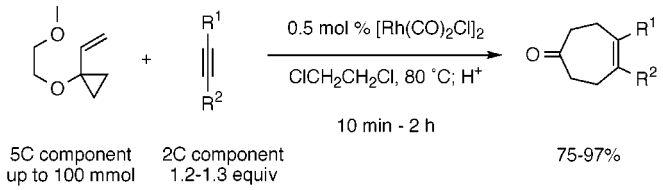
ABSTRACT

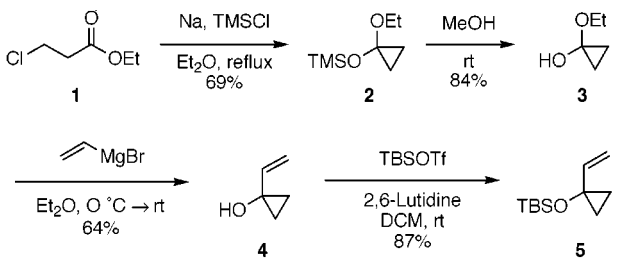


Described herein is an efficient preparative scale synthesis of 1-(2-methyoxyethoxy)-1-vinylcyclopropane and the investigation of the utility of this reagent as a new five-carbon component in metal-catalyzed [5 + 2] cycloadditions. A new cycloaddition procedure is also described that proceeds up to 12-fold faster and with 10-fold less catalyst than previously described, providing cycloheptenones in many cases in minutes and in *isolated* yields of 75–97%. The procedure is readily conducted on a small or large scale (up to 100 mmol thus far).

Transition metal-catalyzed cycloaddition reactions have become exceptionally valuable tools for the preparation of complex synthetic targets.[1] Recent studies from our own program in this area have provided the first examples of metal-catalyzed intra- and intermolecular [5 + 2] cycloadditions between vinylcyclopropanes and π-systems,[2] providing a new reaction and attendant strategies for the synthesis of biologically significant natural and designed compounds containing seven-membered rings.[3] In this Letter, we describe an efficient procedure for the preparation of 1-(2-methyoxyethoxy)-1-vinylcyclopropane (**9**) and investigate the utility of this new five-carbon component in the [5 + 2] cycloaddition.

In 1998, we reported the first examples of rhodium-catalyzed intermolecular [5 + 2] cycloadditions for the synthesis of substituted cycloheptenones.[4] This procedure is based on readily available alkynes as the starting two-carbon component and siloxyvinylcyclopropane **5** as the five-carbon component. Preparing reagent **5** in our previous work involved four steps (Scheme 1).[5] While this reagent and procedure is adequate for many applications, a shorter route that avoided reactive metals and the cost of silyl protecting groups was desired for many anticipated applications.

Scheme 1



(1) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996,** *96*, 49−92. Frühauf, H.-W. *Chem. Rev.* **1997**, *97*, 523−569. Dell, C. P. *J. Chem. Soc., Perkin Trans. 1* **1998,** 3873−3905. Wender, P. A.; Miller, B. L. Toward the Ideal Synthesis: Connectivity Analysis and Multibond-Forming Processes. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; JAI Press: Greenwich, CT, 1993; Vol. 2, pp 27−66. Wender, P. A.; Handy, S. T.; Wright, D. L. *Chem. Ind.* **1997**, 765−769.

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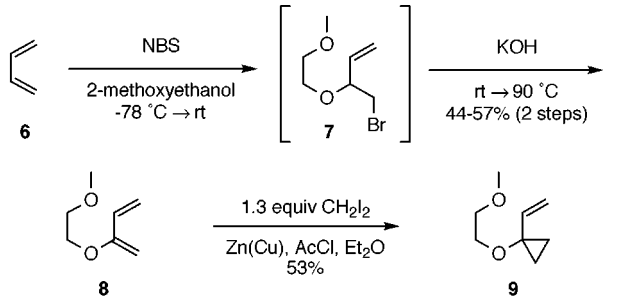
We have now developed a significantly simplified two-step synthesis of alkoxyvinylcyclopropanes that is based on relatively inexpensive reagents and can be conducted safely on a multigram scale. The procedure is illustrated for the preparation of 1-(2-methyoxyethoxy)-1-vinylcyclopropane (**9**). The selection of the methoxyethyl group is based on cost and volatility considerations. This ether is less volatile and therefore easier to use than the corresponding methyl and ethyl ethers, and 2-methoxyethanol is relatively inexpensive. In an optimized procedure 1,3-butadiene (**6**) was monobrominated using *N*-bromosuccinimide[6] with concomitant incorporation of an equivalent of the solvent, 2-methoxyethanol, to produce bromo ether intermediate **7**. In situ dehydrohalogenation was accomplished by portionwise addition of 2.2 equiv of KOH[7] to give **8** in 44−57% isolated yield.[8] Modified Simmons−Smith conditions were used to effect selective cyclopropanation of the more electron rich double bond of **8** in 53% yield.[9] These reactions have been regularly conducted in our laboratories on a multigram scale (Scheme 2). This modified synthesis allows access to

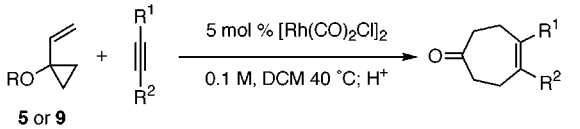
Scheme 2



9 in 30% overall yield at less than one-tenth the cost per mole of generating **5** and without the use of highly reactive metals.[10] In addition, methoxyethyl ethers **8** and **9** can be readily purified by vacuum distillation and are sufficiently nonvolatile to minimize evaporative losses during weighing and handling.

With the availability of the new five-carbon reagent **9**, the next issue to be addressed was its performance relative to reagent **5** in [5 + 2] cycloadditions. The comparison of reagents **5** and **9** in the [5 + 2] cycloaddition is presented in Table 1.[5] Vinylcyclopropane **9** clearly functions as a competent substrate for these cycloadditions, giving in these unoptimized procedures comparable cycloadduct yields at somewhat longer reaction times.

Table 1. Comparison of [5 + 2] Cycloadditions of **5** and **9**



5 or **9**

entry	alkyne[a]	R = TBS (**5**) (yield / time)	R = $CH_3OCH_2CH_2$ (**9**) (yield / time)
1.	H—≡—E	93% / 2 h	76% / 2.5 h
2.	E—≡—E	90% / 2 h	73% / 12 h
3.	H—≡—H	79% / 6 h	89% / 6h
4.	H—≡—OH	74% / 1.5 h	86% / 3 h
5.	H—≡—OMe	88% / 1.5 h	90% / 2.5 h

[a] E = CO_2Me

In an effort to determine whether the reaction rates with **9** could be increased, changes in the reaction conditions were explored. Toward this end, the use of 1,2-dichloroethane instead of dichloromethane was found to be beneficial and a temperature increase from 40 to 80 °C was tolerated without decomposition of the catalyst or reagents. The combined changes proved to be of significant benefit: the cycloaddition of **9** with methyl propargyl ether (1.3 equiv) in the presence of only 0.5 mol % of $[Rh(CO)_2Cl]_2$ in DCE at 80 °C was complete within 15 min and provided upon hydrolysis of the resulting enol ether cycloadduct (1% HCl/MeOH) cycloheptenone **14** in 92% isolated yield (Table 2, entry 5). *Compared to our previous results, this represents*

(2) Wender, P. A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc.* **1995**, *117*, 4720−4721. Wender, P. A.; Husfeld, C. O.; Langkopf, E.; Love, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 1940−1941. Wender, P. A.; Husfeld, C. O.; Langkopf, E.; Love, J. A. Pleuss, N. *Tetrahedron* **1998**, *54*, 7203−7220. Wender, P. A.; Rieck, H.; Fuji, M. *J. Am. Chem. Soc.* **1998**, *120*, 10976−10977. Wender, P. A.; Sperandio, D. *J. Org. Chem.* **1998**, *63*, 4164−4165. Wender, P. A.; Glorius, F.; Husfeld, C. O.; Langkopf, E.; Love, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 5348−5349. Wender, P. A.; Fuji, M.; Husfeld, C. O.; Love, J. A. *Org. Lett* **1999**, *1*, 137−139. Wender, P. A.; Dyckman, A. J.; Husfeld, C. O.; Kadereit, D.; Love, J. A.; Rieck, H. *J. Am. Chem. Soc.* **1999**, *121*, 10442−10443. For recent studies from other laboratories see: Gilbertson, S. R.; Hoge, G. S. *Tetrahedron Lett.* **1998**, *39*, 2075−2078. Binger, P. Wedemann, P. Kozhushkov, S. I. de Meijere, A. *Eur. J. Org. Chem.* **1998**, 113−119. Trost, B. M.; Toste, F. D.; Shen, H. *J. Am. Chem. Soc.* **2000**, *122*, 2379−2380.

(3) Wender, P. A.; Fuji, M.; Husfeld, C. O.; Love, J. A. *Org. Lett.* **1999**, *1*, 137−139.

(4) Wender, P. A.; Rieck, H.; Fuji, M. *J. Am. Chem. Soc.* **1998**, *120*, 10976−10977.

(5) Preparation of **5** by analogy to the methods in the following: Salaün, J.; Marguerite, J. *Org. Synth.* **1985**, *63*, 147−153. Wasserman, H. H.; Hearn, M. J.; Cochoy, R. E. *J. Org. Chem.* **1980**, *45*, 2874−2880.

(6) Overman, L. E.; Kakimoto, M.; Okazaki, M. E.; Meier, P. G. *J. Am. Chem. Soc.* **1983**, *105*, 6622−6629. Original work using *N*-bromosulfonamides: Petrov *J. Gen. Chem. U.S.S.R.* **1938**, *8*, 208−212.

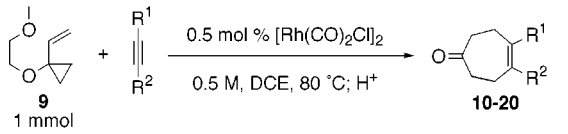
(7) *Caution.* It is important to add the KOH slowly due to the exothermic nature of the reaction causing excess 1,3-butadiene to rapidly boil out of solution at approximately 40 °C.

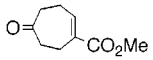
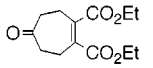
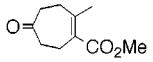
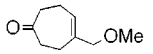
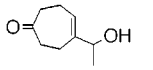
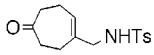
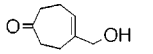
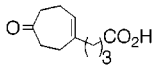
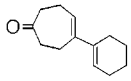
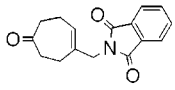
(8) In a representative procedure, *N*-bromosuccinimide (100 g, 0.56 mol) and 2-methoxyethanol (560 mL) are added to a two-neck round-bottom flask under a nitrogen atmosphere. The suspension is cooled to −78 °C at which point condensed 1,3-butadiene (60 mL, 0.75 mol) is added. The reaction is allowed to warm to rt with vigorous stirring. After 16 h to the now clear and colorless solution is added portionwise KOH (85%, 82 g, 1.24 mol) (see safety note, ref 7). The mixture turns a deep red color and reaches 90 °C due to the exothermic nature of the reaction. Upon cooling to rt, the reaction is diluted with 400 mL of water. The product is extracted using pentane (4 × 250 mL). The combined pentane extract is washed with brine, dried ($MgSO_4$), filtered, and condensed by rotoary evaporation. Distillation of the product (10 torr, 60 °C) affords diene **7** in 44−57% yield as a colorless oil.

(9) Friedrich, E. C.; Lewis, E. J. *J. Org. Chem.* **1990**, *55*, 2491−2494.

(10) On the basis of the price of reagents purchased from Aldrich in 1999, **9** cost $211.88/mol ($1.49/g) and **5** cost $2785.25/mol ($14.04/g).

Table 2. Optimized [5 + 2] Cycloadditions of **9** with Alkynes

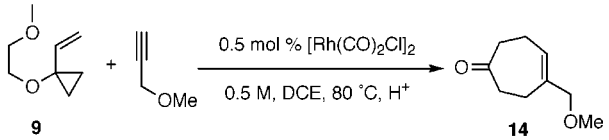


entry	alkyne	time/ yield	product
1.	H—≡—CO_2Me	10 min / 84%	**10** 
2.	EtO_2C—≡—CO_2Et	1 h / 96%	**11** 
3.	—≡—CO_2Me	2 h / 81%	**12** 
4.	H—≡—H	2 h / 75%	**13** 
5.	H—≡—OMe	15 min / 92%	**14** 
6.	H—≡—OH	12 min / 89%	**15** 
7.	H—≡—NHTs	15 min / 87%	**16** 
8.	H—≡—OH	25 min / 82%	**17** 
9.	H—≡—CO_2H	1.5 h / 87%	**18** 
10.	H—≡—	7 h (rt) / 85%	**19** 
11.	H—≡—	11 min / 97%	**20** 

a 6-fold increase in reaction rate using a 10-fold decrease in catalyst loading. Similar results were observed with a variety of alkynes under these reaction conditions with rate increases of as much as 12-fold for some substrates (e.g., entry 1) (Table 2).[11] Significantly, as demonstrated for 1-ethynylcyclohexene (Table 2, entry 10), these reactions can be conducted at room temperature. It is also noteworthy that reactive functionality such as unprotected alcohols and even carboxylic acids are tolerated in this cycloaddition.

The process is also readily scaled. Increasing the reaction scale by 10- and 100-fold gave comparable isolated yields with only a slight increase in reaction time (Table 3). *For example, 14.20 g (100 mmol) of* ***9*** *was converted to 14.52 g (94.1 mmol, 94%) of* ***14*** *in 30 min with 0.5 mmol (192 mg) of catalyst in only 200 mL of solvent.*

Table 3. Scale Study of the [5 + 2] Cycloaddition



entry	scale **9**	time	yield
1.	1 mmol	15 min	92%
2.	10 mmol	25 min	88%
3.	100 mmol (14.20 g)	30 min	94%

In summary, a new reagent (**9**) for metal-catalyzed [5 + 2] cycloadditions is described. This reagent is readily prepared in a concise and cost-effective procedure that can be conducted on a large scale. It is also easily purified and handled. It performs well in a wide range of [5 + 2] cycloadditions. Its use in cycloadditions conducted in 1,2-dichloroethane at 80 °C provides cycloadducts in many cases in minutes and in high yields with minimal catalyst loading. The reagent can be used with a variety of alkyne substrates including those incorporating alcohols and even carboxylic acids. The availability of **9** in conjunction with optimized reaction conditions has enabled the practical, multigram preparation of a variety of substituted cycloheptenones, compounds of use as synthetic building blocks and as scaffolds for combinatorial synthesis.

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Supporting Information Available: IR, NMR, and mass spectroscopy data for compounds **8**−**20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) **General procedure:** To an oven-dried, argon-purged Schlenk flask were added $[Rh(CO)_2Cl]_2$ (1.9 mg, 0.005 mmol) and anhydrous 1,2-dichloroethane (2 mL) under an argon atmosphere. To this was added **9** (142.2 mg, 1 mmol), followed by addition of the alkyne (1.2−1.3 mmol). The flask was placed in an oil bath preheated to 80 °C. The reaction was monitored by TLC. Upon completion, the initially pale yellow solution turned dark red in color. The reaction mixture was treated with 1% HCl in MeOH (0.2 mL). The resultant mixture was filtered through a short pad of silica gel (Et_2O eluant) and concentrated in vacuo. The residue was purified by flash column chromatography.