

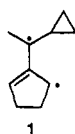
Hydrogen Atom Transfer Reactions to Trimethylenemethane Diyls. A New Reactivity Pattern Leading to Bicyclic Ring Systems¹

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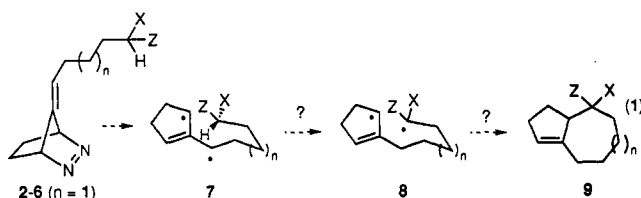
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In the diyl trapping reaction, an alkene, alkyne, or heteroatom-containing unsaturated unit intercepts a trimethylenemethane-like (TMM) diradical in an inter- or an intramolecular [3 + 2] cycloaddition.² This process has proven useful in the construction of a variety of ring systems, particularly that of the linearly fused tricyclopentanoid skeleton.³ Many different solvents have been utilized, including acetonitrile, THF, 2-methyltetrahydrofuran, methanol, and ethylene glycol.^{2,3} In no instance has hydrogen atom abstraction from solvent been documented. That TMM diyls are capable of engaging in such a process was recently demonstrated by Adam and Finzel.⁴ They reported that, in the presence of 0.1 M 1,4-cyclohexadiene as a hydrogen atom donor, diyl **1** is converted to products resulting from hydrogen abstraction in 28% yield.



At the time of their report, we were examining the process portrayed in eq 1. Our idea was to explore atom transfer in a setting designed so that, following intramolecular transfer,⁵ the new radical center would be stabilized by the substituents X and Z and be positioned to engage in carbon-carbon bond formation leading to **9**. The geometry portrayed in **7** ($n = 1$) is very similar to that often associated with the transition-state structure for the intramolecular diyl trapping reaction;^{2,3,5a} it appears ideally suited for atom transfer. The overall process illustrated in eq 1 could be of synthetic utility as it is easy to imagine the conversion of **9** or related materials to a variety of natural products.



(1) Little, R. D.; Billera, C. F. *Abstracts of Papers, 205th National Meeting of the American Chemical Society, Denver, CO; American Chemical Society: Washington, DC, 1993; ORGN 103.*

(2) (a) Little, R. D.; Bode, H.; Stone, K. J.; Wallquist, O.; Dannecker, R. *J. Org. Chem.* **1985**, *50*, 2400. (b) Little, R. D.; Masjedizadeh, M. R.; Moeller, K. D.; Dannecker-Doerig, I. *Synlett* **1992**, 107. (c) Masjedizadeh, M. R.; Fite, C.; Little, R. D. *Tetrahedron Lett.* **1990**, *31*, 1229. (d) Little, R. D. [3 + 2] cycloadditions—thermal. In *Comprehensive Organic Chemistry, Combining C-C π -Bonds*, Trost, B. M., Paquette, L. A., Eds.; Pergamon: Oxford, 1991; Vol. 5, Chapter 3.

(3) Van Hijfte, L.; Little, R. D.; Petersen, J. L.; Moeller, K. D. *J. Org. Chem.* **1987**, *52*, 4647.

(4) (a) Adam, W.; Finzel, R. *J. Am. Chem. Soc.* **1992**, *114*, 4563. (b) We have recently discovered that TMM diyls are capable of initiating DNA cleavage; hydrogen abstraction may be involved. See: Bregant, T. M.; Groppe, J.; Little, R. D. *J. Am. Chem. Soc.* **1994**, *116*, 3635.

(5) (a) For an excellent discussion of atom transfer, the geometric requirements, polar effects, the correlation between bond dissociation energy and transferability, etc., refer to the following: Curran, D. P.; Shen, W. *J. Am. Chem. Soc.* **1993**, *115*, 6051. (b) Curran, D. P. *Synthesis* **1988**, 417 (Part I), 489 (Part II).

Table 1

diazene	X	Z	radical	BDE(C-H), ^a kcal/mol
2	OH	H	$\cdot\text{CH}_2\text{OH}$	94.0
3	H	CN	$\cdot\text{CH}_2\text{CN}$	92.9
4	OMe	OMe	$\cdot\text{CH}(\text{OH})_2$	91.9
5	OH	CO ₂ Me	$\cdot\text{CH}(\text{OH})\text{CO}_2\text{H}$	84.8
			$[\cdot\text{CH}(\text{OH})\text{CHO}]$	[79.1]
6	OTMS	CN	$\cdot\text{CH}(\text{OH})\text{CN}$	82.6

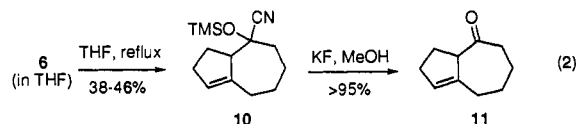
^a Calculated for formation of the radical indicated.

The need to use care in the selection of X and Z was dictated by the realization that abstraction results in a loss of TMM delocalization energy (compare **7** with **8**), particularly so if a planar triplet is involved (see below). The plan was to choose substituents which might compensate for the loss and allow atom transfer to compete with diyl dimerization. We are pleased to report the results of studies establishing the viability of atom transfer within the context of TMM chemistry.

Diyl precursors **2-6** and **13** (see later) were examined. In choosing these systems, we were guided by the C-H bond dissociation energy values of Leroy [BDE(C-H)]⁶ and by the desire that the substituents ultimately be of synthetic utility. Salient BDE values are presented in Table 1.

Neither one or two electron-donating groups (compounds **2** and **4**) nor one electron-withdrawing unit (diazene **3**) is sufficient to facilitate atom transfer. Thus, we found that the diyls derived from diazenes **2**, **3**, and **4** do not engage in atom transfer. Diyl dimerization occurs instead, even when the diazene is added by syringe pump to a solution of refluxing solvent to minimize the diyl concentration. From the information presented in the table, we suggest that when BDE(CH) \geq 90 kcal/mol, atom transfer to a TMM diyl will not occur.

We turned our attention to systems bearing both an electron-withdrawing and an electron-donating substituent. The thought was that since such systems lead to a captodative radical,⁷ the resulting stabilization might be sufficient to reduce the kinetic barrier and permit the desired transformation to occur. The first positive indication arose upon investigation of the trimethylsilyl cyanohydrin **6**. Thus, the syringe pump addition of **6** at a standardized rate of 2×10^{-5} mol/h to refluxing THF afforded a mixture of diastereomeric adducts **10** in yields ranging from 38% to 46%.^{8,9} Treatment of the crude reaction mixture with potassium fluoride in methanol resulted in near quantitative conversion to ketone **11**. The appearance of an infrared absorption



at 1705 cm^{-1} confirmed the presence of a carbonyl in the seven-membered ring. That the absorption did not correspond to a

(6) (a) Leroy, G.; Sana, M.; Wilante, C. *J. Mol. Struct. (Theochem)* **1991**, *234*, 303. (b) Leroy, G. *J. Mol. Struct. (Theochem)* **1988**, *168*, 77. (c) Zhang, X.-M.; Bordwell, F. G. *Acc. Chem. Res.* **1993**, *26*, 510. (d) Leroy, G.; Peeters, D.; Sana, M.; Wilante, C. In *Substituent Effects in Radical Chemistry*; Viehe, H. G.; Janousek, Z.; Merenyi, R., Eds.; Kluwer Academic Press: Dordrecht, The Netherlands, 1986; Chapter 1.

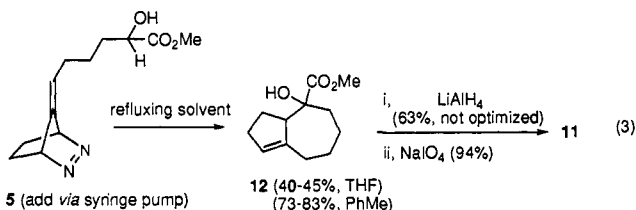
(7) (a) Dewar, M. J. S. *J. Am. Chem. Soc.* **1952**, *74*, 3353. (b) Bordwell, F. G.; Lynch, T.-Y. *J. Am. Chem. Soc.* **1989**, *111*, 7558. (c) Viehe, H. G.; Merenyi, R.; Janousek, Z. *Pure Appl. Chem.* **1988**, *60*, 1635. (d) Sustmann, R.; Korth, H.-G. In *Advances in Physical Organic Chemistry*; Bethell, D., Ed.; Academic Press: San Diego, 1990; Vol. 26, p 131.

(8) (a) This addition rate was used in all cases, unless indicated otherwise. (b) No improvement was observed when the bulky dimethyl *tert*-butylsilyl group was used.

(9) Significant effort was expended to characterize the remainder of the mass balance, but to no avail. For some reason we do not understand, this case was unusually complex, particularly when compared with the hydroxy ester diazene **5**. We know that the material does not correspond to diyl dimers since treatment with KF/MeOH failed to afford aldehyde absorptions (¹H NMR and IR).

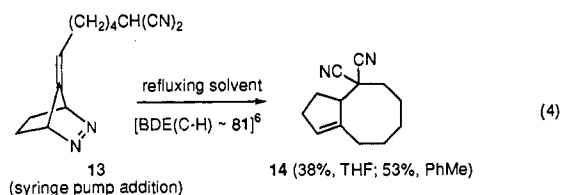
conjugated ketone was confirmed by the presence of a single vinyl proton in the ^1H NMR spectrum, and by observation of the expected number and type of carbon signals in the APT ^{13}C NMR spectrum.

A similar yield of a 1:1 mixture of diastereomeric atom transfer derived adducts **12** was obtained when hydroxy ester **5** was subjected to the same conditions (40–45% **12**, ~40% diyl dimer).^{8a}



The α -hydroxy ester functionality in **12** was conveniently converted to a carbonyl unit in the manner illustrated (not optimized). A dramatic improvement was observed when the reaction of hydroxy ester **5** was conducted in refluxing toluene; yields of 73–83% were obtained consistently (~10% diyl dimers). Note eq 3.

When the dinitrile diazene **13** was added by syringe pump to refluxing toluene, a 53% yield of the [6.3.0] adduct **14** was obtained; in refluxing THF, the yield dropped to 38%. The ability of the atom-transfer process to generate an eight-membered ring via a 1,6-hydrogen transfer is noteworthy and may prove of synthetic utility.¹⁰



We suggest that the temperature effect observed in both of these cases may simply indicate that the rate of atom transfer changes faster with temperature than does the rate of diyl dimerization.^{11,12} Indeed, it is generally accepted that the rate constants for radical–radical combination have only a small temperature dependence.¹² That the effect is due to temperature

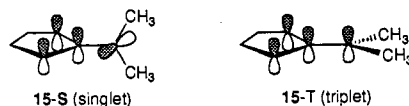
(10) Huang, X. L.; Dannenberg, J. J. *J. Org. Chem.* **1991**, *56*, 5421.

(11) Little, R. D.; Billera, C. F. *Tetrahedron Lett.* **1988**, *29*, 5711. From this work, we conclude that the half-life of a typical monoalkyl-substituted diazene is ~0.6 h at 65 °C and ~11 s at 110 °C.

(12) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon: Oxford, 1986; p 12.

and is not associated with the possibility that toluene is an atom-transfer agent was clarified by conducting the conversion of **5** to **12** in *n*-octane (bp 126 °C) under otherwise identical reaction conditions. While octane is not a good hydrogen atom donating solvent, the same products were obtained and within experimental error, in the same yields.^{13,14 a}

We believe that the triplet diyl is the reactive species in the atom-transfer process. While trimethylenemethane singlets are generally thought to be bisected and therefore potentially more reactive than the planar, fully delocalized triplet diyl, it is unlikely that the singlet survives long enough to play a role.^{13,15} The lifetime of the initially formed singlet is limited by the rate of intersystem crossing ($S \rightarrow T$), a process which for the dimethyl diyl **15-S** is *ca.* 10^8 s^{-1} .^{13b,15} That we are able to obtain atom-



transfer products only when the reaction conditions also favor dimerization, coupled with the realization that dimerization occurs *via* the combination of two triplets, suggests that atom transfer is also triplet derived.

In summary, we have described the first examples of intramolecular hydrogen atom transfer by a TMM diradical. The sequence quickly assembles the [5.3.0] and [6.3.0] ring systems. It holds promise as a potential route to natural products, and it awaits mechanistic exploration. Efforts to do so are in progress.

Acknowledgment. We are very grateful to the National Cancer Institute of the National Institutes of Health for their support of this research.

Supplementary Material Available: General procedure for atom transfer and a summary of NMR spectra (^1H and ^{13}C -APT) for **5**, **6**, and **11–14** (2 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(13) The short lifetime of the singlet precludes reaction with any typical organic solvent. (a) Kelley, D. F.; Rentzepis, P. M. *SPIE, Picosecond Lasers Appl.* **1982**, *322*, 206. (b) Kelley, D. F.; Rentzepis, P. M.; Mazur, M. R.; Berson, J. A. *J. Am. Chem. Soc.* **1982**, *104*, 3764.

(14) (a) The second-order rates for hydrogen transfer to and from solvent are too slow to compete with intersystem crossing from singlet to triplet diyl. For an excellent discussion of radical reaction kinetics and a tabulation of many rate constants, refer to the following: Newcomb, M. *Tetrahedron* **1993**, *49*, 1151. (b) Newcomb, M.; Park, S. U. *J. Am. Chem. Soc.* **1986**, *108*, 4132.

(15) Berson, J. A. In *Diradicals*; Borden, W. T., Ed.; Wiley: New York, 1982; Chapter 4, p 154.