ORGANIC LETTERS

1999
Vol. 1, No. 5
693−696

Radical Additions of TEMPO to Ketenes: Correlation of Free Radical and Nucleophilic Reactivity

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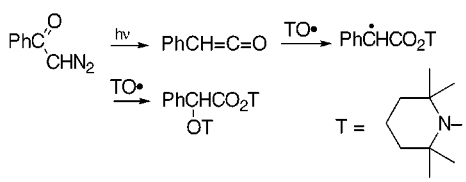
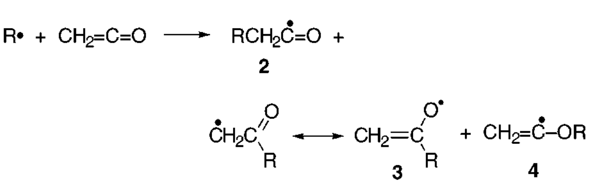
Received April 30, 1999

ABSTRACT



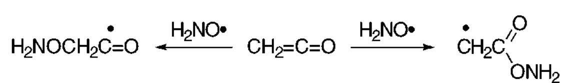
Tetramethylpiperidinyloxy (TEMPO, TO•) reacts with a variety of ketenes $R^1R^2C{=}C{=}O$ by rate-limiting attack on carbonyl carbon to give the 1,2-bis(adducts) $R^1R^2C(OT)CO_2T$. The α,β-unsaturated ketenes (*E*)-PhCH═CHCH═C═O (8b) and PhC≡CCH═C═O (8c) give the 1,4-bis(adducts) PhCH(OT)CH═CHCO$_2$T and PhC(OT)═C═CHCO$_2$T. The ketenes may be generated *in situ* for these reactions in the presence of TEMPO by either dehydrochlorination of $R^1R^2CHCOCl$ with Et_3N or Wolff rearrangement. Ketenes PhCH═C═O (8a), 8b, and 8c had not previously been observed as long-lived species at room temperature, but when formed by photochemical Wolff rearrangement, these could be characterized in solution by conventional IR spectroscopy and used for kinetic studies for reaction with TEMPO using UV detection. The reactions of six ketenes with TEMPO in hydrocarbon solvents follow second-order kinetics, with a range of 2.5×10^5 in the rate constants, which are correlated with unit slope with the corresponding rate constants for hydration.

Free radical additions to ketenes[1,2] have received only scattered attention since the original observation by Staudinger that Ph$_2$C═C═O (**1**) was sensitive to O$_2$, which implies that ketenes are reactive with free radicals. Recent theoretical studies[2a] at the B3LYP/6-31G*//B3LYP/6-31G* level of the possible reaction pathways shown in eq 1 support this



(1)

expectation and predict that the formations of acyl radicals **2** and enolic radicals **3** are exothermic by 32.6 and 54.7 kcal/mol, respectively, for HO• attachment. For the aminoxyl radical H$_2$NO• attack at CH$_2$ is predicted to be endothermic by 7.5 kcal/mol, while carbonyl carbon attack is exothermic by 18.7 kcal/mol (eq 2).[2b]



(2)

Experimental studies with the stable free radical 2,2,6,6-tetramethylpiperidinyloxy (TEMPO, TO•) have confirmed these predictions.[2b] Thus, the persistent ketene Ph$_2$C═C═O reacts readily with TEMPO, and exposure of the product to O$_2$ gives peroxide **6** by the proposed mechanism shown (eq 3), while the bisketene (Me$_3$SiC═C═O)$_2$ (**7**)[2c] and TEMPO form bis(trimethylsilyl) maleic anhydride.[2b]

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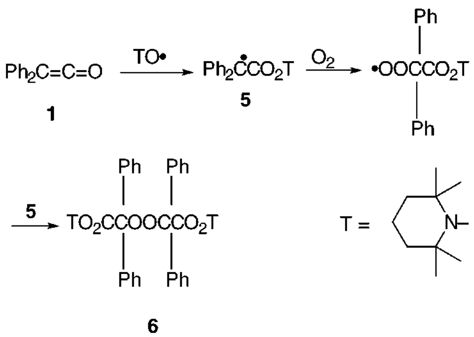
10.1021/ol990628i CCC: $18.00
Published on Web 08/08/1999

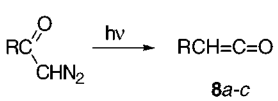


(3)

The use of nitroxyl radicals as radical traps is widely practiced,[3−5] and the examination of their reactions with nonradical species is also attracting increasing attention. Thus, the kinetics of hydrogen abstraction from various substrates by $(CF_3)_2NO^\bullet$ have been measured,[4a] and TEMPO has been found to abstract H atoms from methylbenzenes at 120 °C.[4b] The reversible reactions of TEMPO with benzyl radicals have also found extensive application in living free radical polymerization.[5]

There have been many recent kinetic studies of radical additions to alkenes,[6] and the discovery[2b] of the reaction of TEMPO with $Ph_2C{=}C{=}O$ and with the bis(ketene) **7** suggests an opportunity to extend the study of TEMPO reactions to include other ketenes and activated alkenes. Reported herein are our studies of the scope of the reaction with ketenes, which also reveal that a number of highly reactive ketenes may be generated by Wolff rearrangement for direct observation using conventional spectroscopy at ambient temperature.

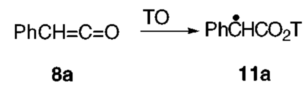
Phenylketene (**8a**) is the prototype of a reactive, nonpersistent ketene and was first generated by Zn dechlorination of PhCHClCOCl by Staudinger in 1911.[7a] However, strenuous efforts to isolate this ketene were unsuccessful, although there was evidence from trapping experiments of its presence in solution.[7a] Since that time this ketene has been generated in situ for preparative or mechanistic studies, including cycloadditions,[7b] hydration,[7c] and amination.[7d] Wolff rearrangement of diazoketones such as **9a**−**c** provides a convenient route to highly reactive ketenes such as **8a**−**c**.



(4)

9*a-c* (*a*, R = Ph; *b*, R = *E*-PhCH=CH; *c*, R = PhC≡C)

Diazoacetophenone (**9a**) proved to be a suitable precursor of $PhCH{=}C{=}O$ (**8a**) for in situ trapping with TEMPO, as **9a** was inert to TEMPO at room temperature but upon refluxing of the mixture in toluene gave the adduct **10a** of 1,2-addition of two TEMPO molecules (eq 5). The structure

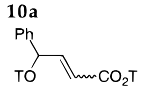
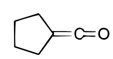
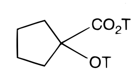
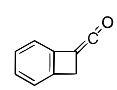
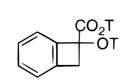


(5)

of **10a** follows from the spectral properties, including the C=O band in the IR at 1750 cm^{-1}, and the ^{1}H NMR spectrum, with the CHO signal at δ 5.23, and there are eight cleanly resolved CH_3 singlets, as expected not only due to the conformational properties of the piperidinyloxy groups[8] but also to the diastereotopic nature of the CMe_2 units. The structure of **10a** was confirmed by its X-ray structure. Initial attack of TEMPO on the carbonyl carbon of **8a** to give the enolic radical **11a** is expected by analogy with the results from $Ph_2C{=}C{=}O$ (eq 3), followed by capture by the second TEMPO molecule as documented for other enolic radicals.[4c] Generation of the 1-naphthyl analogue of **8a** by Wolff rearrangement and trapping as the TEMPO adduct corresponding to **10a** has also been reported.[2d]

The photochemical Wolff rearrangement of diazoketones **9b**,[9b] **9c**,[9a] and others[10a,11] to give ketenes **8b**,[9a] **8c**,[9a] **12**,[10b] and **13**[11] for trapping with TEMPO was also successful and led to the bis(adducts) **10b,c**, **14**, and **15** (Table 1).[12]

Table 1. Capture of Ketenes by TEMPO

Ketene (IR)	Product	(yield)^a
PhCH=C=O **8a** 2117 cm^{-1} (lit[7d] 2118 cm^{-1})	PhCH(OT)CO_2T **10a**	(45%)
E-PhCH=CHCH=C=O **8b** 2116 cm^{-1} (lit[7d] 2116 cm^{-1})	 **10b**	(28%)[c]
PhC≡CCH=C=O **8c** 2131 cm^{-1} (lit[7d] 2132 cm^{-1})	PhC(OT)=C=CHCO_2T **10c**	(29%)
 **12** (2106, 2122 cm^{-1})^b	 **14**	(35%)
 **13**	 **15**	(27%)

^{a} Yields not optimized. ^{b} Similar spectrum published in ref 10b. ^{c} Reference 12.

The dehydrochlorination of acyl chlorides with Et_3N is a long established route to ketenes,[1a] and this procedure carried

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out in the presence of TEMPO also proved successful for the in situ trapping of ketenes (eq 6).

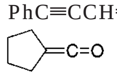
$$\mathrm{RCH_2COCl} \xrightarrow{\mathrm{Et_3N}} \underset{\mathbf{8a,b,d,e}}{\mathrm{RCH{=}C{=}O}} \xrightarrow{\mathrm{2TO^\bullet}} \underset{\mathbf{10a,b,d,e}}{\mathrm{RCH(OT)CO_2T}} \qquad (6)$$

R = Ph, **8a**, **10a** (30%); R = PhCH=CH, **8b**, **10b** (28%); R = *t*-Bu,[13a−c] **8d**, **10d** (16%); R = PhO,[3d] **8e**, **10e** (58%)

Kinetic studies of amination[7d] and hydration[7c,9a] of reactive ketenes, including **8a−c**, were previously carried out using in situ generation of the ketenes by Wolff rearrangement using flash photolysis of diazo ketones. However, this methodology may be complicated for studies of ketene reactions with TEMPO, which has a strong UV/visible chromophore. We have circumvented this obstacle by finding that solutions of these ketenes may be generated separately by Wolff rearrangements in hydrocarbon solvents, and these are surprisingly long-lived, permitting their spectral characterization and use. Thus, photolysis of diazo ketones **9a−c** and 2-diazocyclohexanone in isooctane gave solutions of ketenes **8a−c** and **12**, whose characteristic ketenyl IR bands (Table 1) and UV spectra could be measured by conventional means and are in good agreement with literature results.

Measurement of the rates of reaction of the long-lived ketenes **1** and **7** with excess TEMPO was successful, as determined by observation of the decrease in the ketene chromophores by UV (Table 2). Interestingly the theoretically calculated[2a] $\Delta S^\ddagger$ value for attachment of HO• to C_α of CH_2=C=O is −32.3 eu, which is quite close to the value of −29.6 eu found for the reaction of **7** with TEMPO. This is reasonable for these bimolecular reactions proceeding by similar mechanisms.

Table 2. Rate Constants for Ketene Reaction with TEMPO at 25 °C[a]

ketene	k_2^{TEMPO} (M^{-1} s^{-1})
Ph_2C=C=O (**1**)	0.357
$(Me_3SiC{=}C{=}O)_2$ (**7**)	1.50×10^{-4} [b]
PhCH=C=O (**8a**)	1.26
(*E*)-PhCH=CHCH=C=O (**8b**)	18.4
PhC≡CCH=C=O (**8c**)	37.4
	2.98×10^{-2} [c]

[a] In isooctane unless noted. [b] In mesitylene, extrapolated from data at higher temperatures; $\Delta H^\ddagger$ = 13.8 kcal/mol, $\Delta S^\ddagger$ = −29.6 cal K^{-1} M^{-1}. [c] H_2O rate.[13c]

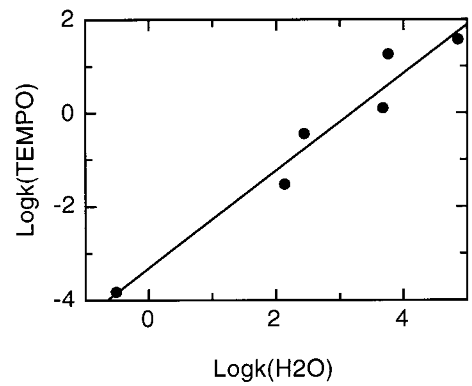


Figure 1. Comparative reactivity of ketenes with TEMPO and H_2O.

Solutions of the ketenes **8a−c** and **12** were prepared by photochemical Wolff rearrangements, and their reaction rates with TEMPO were measured using conventional UV. All the ketenes showed good first-order dependences on [TEMPO]; the derived second-order rate constants are summarized in Table 2, and full kinetic data are given in Table 3 (Supporting Information).

The rate constants for the reactions of the ketenes with TEMPO show a variation of 2.5×10^5 with ketene structure. There have been extensive studies of the hydration reactivities of ketenes in H_2O[2c,7c,9a,13a−c] and for amination in CH_3CN,[7d,14a] and both these reactions also show large variations in reactivity with ketene structure. Theoretical studies of ketene hydration and amination favor rate-limiting in-plane nucleophilic attack on the carbonyl carbon, with hydrogen bonding interactions involving other H_2O or amine molecules coordinating with the nucleophile and the ketenyl oxygen.[1a,14b−e]

The most extensive set of ketene reactivity data is for hydration, and correlation of log k_{TEMPO} for the reaction of the ketenes with TEMPO (25 °C) with the corresponding values of log *k* for hydration in H_2O gives the relationship of eq 7 , as illustrated in Figure 1. The unit slope leads to the interesting conclusion that the reactions of ketenes with

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(12) The product **10b** is obtained as an unseparated 2/1 or 3/1 mixture of *E/Z* isomers by dehydrochlorination or Wolff rearrangement, respectively, as identified by the 2-D ^{1}H and ^{13}C NMR spectra. The yield reported is for the dehydrochlorination route. Products **10c−e**, **14** and **15** are identified by consistent NMR, MS, and IR spectra. See the Supporting Information for details.

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$$\log k_{TEMPO} = (0.98 \pm 0.08) \log k_{H_2O} - (3.30 \pm 0.19) \qquad (7)$$

TEMPO, which involve formation of a C−O bond, correlate with the hydration reactivities, which also involve C−O bond formation.

Attachment of $H_2NO^{\bullet}$ to C_{α} of $CH_2{=}C{=}O$ is calculated[2b] to be 36.0 kcal/mol less favorable than the corresponding attachment of $HO^{\bullet}$,[2a] and experimentally the reaction of TEMPO with ketenes shows appreciable barriers (Table 2). This is consistent with the much lower reactivity calculated for $H_2NO^{\bullet}$ relative to $HO^{\bullet}$ and also with the steric barriers expected for reaction of TEMPO compared with $H_2NO^{\bullet}$.

Acknowledgment. Financial support by the Natural Sciences and Engineering Research Council of Canada and the donation of diazo ketone **9b** by Professor R. Danheiser (MIT) are gratefully acknowledged.

Supporting Information Available: Experimental procedures, kinetic data, NMR spectra, and X-ray structural information on **10a** and an X-ray crystallographic file, in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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