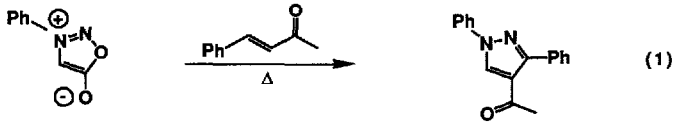
Tetrahedron Letters,Vol.30,No.35,pp 4625-4628,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

CYCLOADDITION OF β-SUBSTITUTED ENONES TO A BICYCLIC SYDNONE: OBSERVATION OF AN UNEXPECTEDLY FACILE HYDROCARBON ELIMINATION

Scott D. Larsen* and Esther Martinborough
Metabolic Diseases Research
The Upjohn Company
Kalamazoo, MI 49001

ABSTRACT: Cycloaddition of β-alkyl- or β-arylenones to bicyclic sydnone **3** in the absence of added oxidant affords mixtures of the tetrahydropyrazolo[1,5-a]pyridines **4** and **5**. The amount of **5** formed was dependent on the nature of R.

The [1,3]-dipolar cycloaddition of sydnones to olefins to form Δ^2-pyrazolines has been known for nearly 30 years.[1,2] Huisgen reported that the addition of an oxidant to the reaction mixture allowed for the direct isolation of pyrazoles.[3] In the same work, it was observed that 4-phenyl-3-buten-2-one reacted with N-phenylsydnone **1** to give pyrazole **2** without the need for added oxidant (eq. 1).

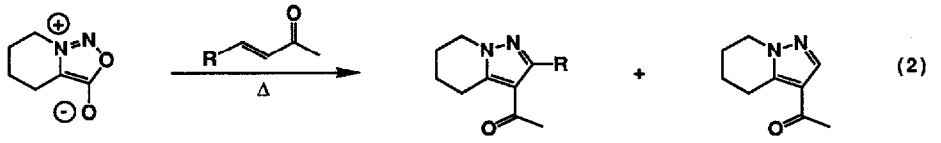


1 **2** (1)

Our requirement for tetrahydropyrazolo[1,5-a]pyridinyl ketones **4** prompted us to explore this reaction further using the known bicyclic sydnone **3**[4] (eq. 2). We have found that cycloaddition of **3** with a variety of 4-alkyl or aryl-3-buten-2-ones does indeed provide the desired bicyclic pyrazoles **4** without the need for added oxidant. We were quite surprised, though, to isolate varying amounts of the unsubstituted pyrazolyl ketone **5**[5] from several of the reactions. The amount of this unexpected side product formed was highly dependent on the nature of the enone β-substitution, as illustrated in Table I.

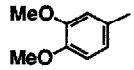
It is evident from the Table that only when alkyl-substituted enones were employed was any **5** isolated, the amount increasing dramatically with greater degrees of substitution within the R group (entries 1 - 4). Use of aryl-substituted enones (entries 5 - 7) led only to the expected products **4**. The reactions all proceeded in good overall yields.

TABLE I [a]



(2)

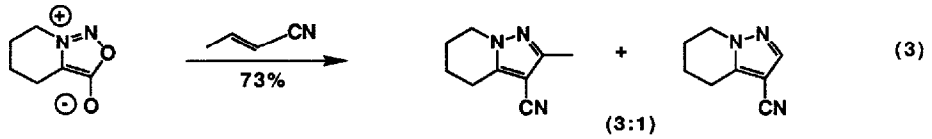
3 **4** **5**

Entry	R	% 4 [b]	% 5 [b]
1	CH_3	61	7
2	n-Pr	20	55
3	i-Pr	7	72
4	$PhCH_2$	12	58
5	Ph	67	0
6		63	0
7		73	0

[a] All reactions were performed in o-xylene (1 M) at reflux using 3 eq. of enone.

[b] Isolated yields following flash chromatography. All new compounds were fully characterized spectrally and had elemental composition established by combustion analysis or high resolution MS.

This unusual hydrocarbon elimination[6] was not limited to enones. Employing crotononitrile (eq. 3) resulted in a mixture of nitriles **6** and **7** in a ratio similar to that obtained with pentenone (entry 1 in Table I).

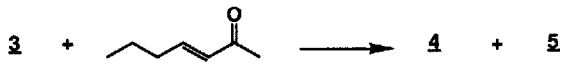


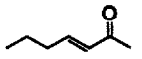
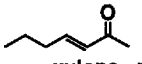
(3)

3 **6** **7**

To gain further insight into the mechanism of this elimination, the cycloaddition to heptenone (entry 2) was examined further. Control experiments established that the loss of the propyl group was not occurring from either the enone or the pyrazole **4**; both materials were recovered unchanged from refluxing xylene. The reaction conditions were modified to determine if the ratio of products would be affected (Table II).

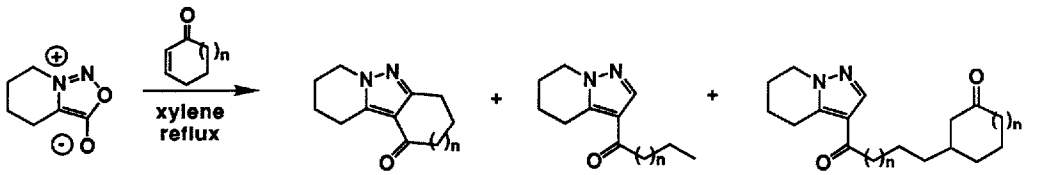
TABLE II



Entry	Conditions	4 : 5
1	xylene, reflux	1 : 2.4
2	benzene, reflux	1 : 1.3
3	CH_3CN, reflux	1 : 1
4	 neat, 145°	1 : 1.3
5	 slow addition, xylene, reflux	1 : 4

It is clear from the Table that both the reaction temperature and the solvent polarity had only minor effects on the product ratio. Furthermore, identical mixtures were obtained regardless of whether the reaction was run under an atmosphere of nitrogen or oxygen. However, varying the concentration of the heptenone did have some effect on the product ratio (entries 4 and 5). Decreasing the effective concentration of the enone increased the proportion of product arising from elimination of the propyl moiety.

Cycloaddition of cycloalkenones to sydnone **3** provided mixtures of products which shed further light on the mechanism of the hydrocarbon elimination (eq. 4). In addition to the anticipated tricyclic product **8**, two ring-cleaved products **9**[5] and **10**[5] were isolated. **10** is particularly noteworthy in that it has incorporated a second molecule of enone, evidently via a Michael addition. Cycloheptenone provided significantly more of the side products than did cyclohexenone.



(4)

3 **8** **9** **10**

	8		9		10	(Total Yield)
n = 2	4	:	1	:	1	(70%)
n = 1	20	:	1	:	1	(65%)

The elimination of hydrocarbon from molecules undergoing aromatization is not an unknown phenomenon.[1,7] However, to the best of our knowledge, this is the first reported example where loss of hydrocarbon has occurred in direct competition with simple hydrogen elimination. The mechanism of this transformation remains unclear. Earlier investigators have speculated that such alkane eliminations are radical-based processes.[7a,b,h] Our observations of lack of solvent effect, the dependence on the nature of the leaving group R, and the isolation of products such as **9** and **10** are all consistent with a process involving loss of R as a radical.

References

1. Huisgen, R.; Gotthardt, H.; Grashey, R. *Ang. Chem. Int. Ed.* **1962**, *1*, 49.
2. Gotthardt, H.; Huisgen, R. *Chem. Ber.* **1968**, *101*, 552.
3. Huisgen, R.; Grashey, R.; Gotthardt, H. *Chem. Ber.* **1968**, *101*, 829.
4. Hammick, D.L.; Voaden, D.J. *J. Chem. Soc.* **1961**, *3303*. This compound was prepared from pipecolinic acid by the method of Ranganathan: Ranganathan, D.; Bamezai, S. *Tet. Lett.* **1983**, *24*, 1067.
5. **5**: ^{1}H NMR ($CDCl_3$, 300 MHz, δ), 7.87 (s, 1H), 4.19 (t, 2H, J = 6 Hz), 3.13 (t, 2H, J = 6 Hz), 2.44 (s, 3H), 1.85-2.15 (m, 4H); IR (mull, cm^{-1}) 1651.
   9 (n = 1): ^{1}H NMR ($CDCl_3$, 300 MHz, δ), 7.84 (1H, s), 4.16 (t, 2H, J = 6 Hz), 3.10 (t, 2H, J = 6 Hz), 2.73 (t, 2H, J = 7 Hz), 1.8-2.1 (m, 4H), 1.65 (m, 2H), 1.38 (m, 2H), 0.94 (t, 3H, J = 7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz, δ) 195.8, 143.2, 140.2, 118.9, 47.9, 40.1, 26.5, 23.4, 22.6, 22.4, 19.3, 13.8; IR (neat, cm^{-1}) 1660.
   10 (n = 1): ^{1}H NMR ($CDCl_3$, 300 MHz, δ) 7.84 (s, 1H), 4.16 (t, 2H, J = 6 Hz), 3.10 (t, 2H, J = 6 Hz), 2.72 (t, 2H, J = 7 Hz), 2.40 (m, 4H), 2.03 (m, 2H), 1.84 (m, 5H), 1.65 (m, 4H), 1.31 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz, δ) 214.2, 195.4, 143.3, 140.2, 118.9, 49.8, 47.9, 43.7, 40.2, 37.0, 36.7, 35.8, 28.4, 26.6, 24.32, 24.26, 23.5, 22.6, 19.3; IR (neat, cm^{-1}) 1700, 1661.
6. "Hydrocarbon elimination" here refers solely to the loss of an alkyl moiety. The actual nature of the fragments lost is not known.
7. a. Elderfield, R. C.; Burgess, K. L. *J. Am. Chem. Soc.* **1960**, *82*, 1975.
   b. Zobian, E. J.; Kelley, W. S.; Dunthan, H. C. *J. Org. Chem.* **1964**, *29*, 584.
   c. Huisgen, R.; Gotthardt, H. *Chem. Ber.* **1968**, *101*, 839.
   d. Huisgen, R.; Grashey, R.; Krischke, R. *Lieb. Ann. Chem.* **1977**, 506.
   e. LeFevre, G.; Hamelin, J. *Tet. Lett.* **1978**, 4503.
   f. Fu, P. P.; Harvey, R. G. *Chem. Rev.* **1978**, *78*, 317.
   g. Sucrow, W.; Rau, D.; Bredthauer, G. *Chem. Ber.* **1980**, *113*, 2028.
   h. Burger, K.; Kahl, T. *J. Fluorine Chem.* **1987**, *36*, 329.

(Received in USA 5 May 1989)