Retro Aza Diels–Alder Reactions of 2-Azanorbornenes: Improved Methods for the Unmasking of Primary Amines

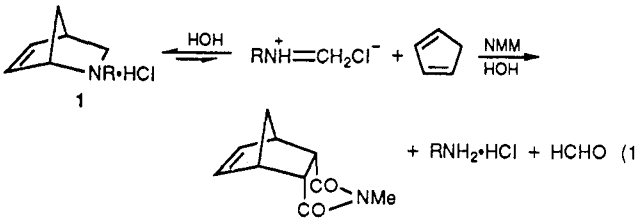
Paul A. Grieco* and Jerry D. Clark

Department of Chemistry, Indiana University, Bloomington, Indiana 47405

Received February 6, 1990

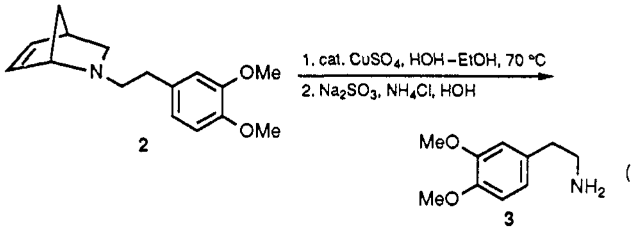
Summary: The unmasking of primary amines via the heterocycloreversion of *N*-alkyl-2-azanorbornenes can be catalyzed by either copper(II) or a sulfonic acid based ion exchange resin which obviates the necessity of employing a reactive dienophile to trap the cyclopentadiene as it is produced.

It has recently been reported[1] that azanorbornenes of type 1 undergo acid-catalyzed retro Diels–Alder reaction in the presence of a reactive dienophile such as *N*-methylmaleimide (NMM) (eq 1), which serves to trap the cyclopentadiene as it is produced, thus driving the heterocycloreversion reaction to completion. We now describe two new methods for effecting the cycloreversion of *N*-alkyl-2-azanorbornenes both of which obviate the necessity of employing a reactive dienophile to trap cyclopentadiene. The first method features a novel copper(II)-catalyzed unmasking of the primary amine. The second method employs a sulfonic acid based ion exchange resin which (1) serves to catalyze the heterocycloreversion process and (2) bind the liberated amine, thereby physically separating the cycloreversion components. Both methods have distinct advantages over the existing methodology.



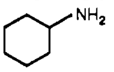
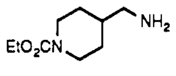
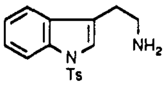
(1)

The copper(II)-catalyzed cycloreversion reactions are best conducted at ca. 70 °C in aqueous ethanol or aqueous methanol. The general process is illustrated below for the cycloreversion of the 2-azanorbornene 2[2] derived from homoveratrylamine (eq 2). A 1.0 M solution of 2 in 50% aqueous ethanol was exposed (70 °C) to 0.05 equiv of copper sulfate. After 2 h, the reaction was cooled to ambient temperature whereupon 0.05 equiv of sodium sulfite was added along with 0.1 equiv of ammonium chloride. After 10 min, homoveratrylamine (3) was isolated in 82% yield by extraction with ether. The use of sodium sulfite serves to remove extraneous copper(II) via reduction to copper(I). The retro Diels–Alder reactions of 2-azanorbornenes do proceed at ambient temperature in the presence of 1 equiv of copper sulfate; however, reactions proceed very slowly.



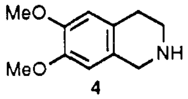
(2)

Table I. Copper Sulfate Catalyzed Retro Aza Diels–Alder Reactions[a]

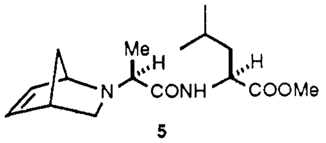
amine	time, h	% yield[b]
$CH_3(CH_2)_4CH_2NH_2$	5.0	99[c]
	7.0	84[c]
$H_2NCH_2(CH_2)_4CH_2NHCO_2Et$	1.0	74
	1.5	85
	2.2	75

[a] All reactions were carried out 0.5 M in 50% aqueous ethanol employing 0.05 molar equiv of copper sulfate. [b] Isolated yields. [c] Isolated as the hydrochloride salt.

The procedure detailed above employing copper sulfate is applicable to a variety of substrates (Table I). The major advantage associated with using copper(II) to catalyze the cycloreversion of 2-azanorbornenes is that the concentration of immonium ion is negligible, thus avoiding potential side reactions with other functional groups within the molecule. For example, in the conventional acid-catalyzed retro Diels–Alder reaction[1] of 2 in the presence of *N*-methylmaleimide (cf. eq 1) ca. 20% of the Pictet–Spengler cyclization product 4 is obtained. However, in the copper(II)-promoted cycloreversion of azanorbornene 2 (eq 2) not a trace of 4 was detected. However the above procedure utilizing copper sulfate is not without its limitations. During attempts to unmask the terminal amine function of simple di- and tripeptide esters (cf. the 2-azanorbornene 5 derived from L-alanyl-L-leucine methyl ester) considerable ester hydrolysis occurs. Detailed below is an alternate procedure which is applicable to a number of systems including di- and tripeptides.



4



5

In order to circumvent the problem of hydrolysis associated with the copper(II)-initiated heterocycloreversion of azanorbornenes derived from amino acids and/or di- and tripeptides, we examined a number of sulfonic acid based ion exchange resins. Best results were obtained with a 2% crosslinked ion exchange resin, Bio-Rad AG 50W-X2, 200–400 mesh. Reactions are generally conducted between 40 and 70 °C, employing 2–3 wt equiv of resin as illustrated in Table II. A typical procedure employing the 2-azanorbornene derivative 6 of L-phenylalanyl-L-leucine methyl ester illustrates the method.

A 0.17 M solution of 6 in water–methanol (1:2) was exposed (2 h) to 2.0 wt equiv of Bio-Rad AG 50W-X2,

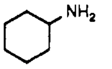
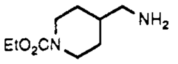
---

[1] Grieco, P. A.; Parker, D. T.; Fobare, W. F.; Ruckle, R. *J. Am. Chem. Soc.* **1987**, *109*, 5859.

[2] For the preparation of 2-azanorbornenes, see: Larsen, S. D.; Grieco, P. A. *J. Am. Chem. Soc.* **1985**, *107*, 1768.

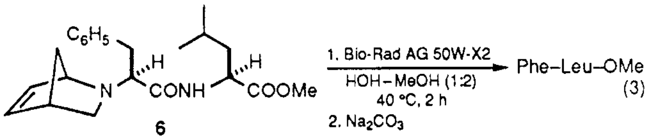
0022-3263/90/1955-2271$02.50/0

Table II. Acid-Catalyzed Retro Aza Diels-Alder Reactions[a]

amine	time, h	temp, °C	% yield[b]
$CH_3(CH_2)_4CH_2NH_2$	5.0	73	97[e]
	7.5	73	94[e]
$H_2NCH_2(CH_2)_4CH_2NHCO_2Et$	3.5	73	87
	1.25	71	91
Leu-OMe	1.0	73	98[e]
Phe-OMe[c]	1.5	45	93
Ser-OMe	1.5	73	87[e]
Ala-Leu-OMe	1.0	73	82
Leu-Leu-Leu-OMe[d]	2.0	70	82
Phe-Phe-Phe-OMe[d]	1.5	45	86

[a] All reactions were conducted 0.17 M in methanol-water (2:1) employing 3.0 wt equiv of Bio-Rad AG 50W-X2, 200–400 mesh, unless stated otherwise. [b] Isolated yields. [c] 2.5 wt equiv of ion-exchange resin were employed. [d] 2.0 wt equiv of ion-exchange resin were employed. [e] Isolated as the hydrochloride salt.

200–400 mesh, ion-exchange[3] resin at 40 °C. After cooling to ambient temperature, the resin was washed with hexanes and neutralized with 10% aqueous sodium carbonate solution. Extraction with ethyl acetate provided L-phenylalanyl-L-leucine methyl ester in 80% yield without any racemization.[4] It is important to note that the success of this heterocycloreversion process is highly dependent upon the percentage of crosslinking in the resin. In our initial study conducted with an 8% crosslinked resin (Dowex 50X8-200), results were disappointing. For example, exposure of 6 to 2 wt equiv of Dowex 50X8-200 using the conditions cited above in eq 3 gave rise after 5 h to only a 47% yield of Phe-Leu-OMe.



(3)

We anticipate that the mildness and efficiency of the procedures detailed above for the unmasking of primary amines will render the 2-azanorbornene structural unit as a useful new protecting group for primary amines.[5]

Acknowledgment. This investigation was supported by a grant from the National Science Foundation. We thank Heidi Berven for experimental assistance during the early stage of this work.

---

[3] The resin was washed sequentially with 1.0 N hydrochloric acid, deionized water (until pH 7.0), and methanol followed by air-drying prior to use.

[4] Any racemization is less than the detection limit which is estimated at 0.06–0.07% (Dewey, R. S.; Schoenewaldt, E. F.; Joshua, H.; Paleveda, W. J., Jr.; Schwam, H.; Barkemeyer, H.; Arison, B. H.; Veber, D. F.; Denkewalter, R. G.; Hirschmann, R. *J. Am. Chem. Soc.* **1968**, *90*, 3254.

[5] For the protection of primary amines, see: Greene, T. W. *Protective Groups in Organic Synthesis*; John Wiley and Sons: New York, 1981. Djuric, S.; Venit, J.; Magnus, P. *Tetrahedron Lett.* **1981**, *22*, 1787. Weinreb, S. M.; Demko, D. M.; Lessen, T. A.; Demers, J. P. *Ibid.* **1986**, *27*, 2099. Overman, L. E.; Okazaki, M. E.; Mishra, P. *Ibid.* **1986**, *27*, 4391.

Photochemical 1,3-Oxygen-to-Carbon Migrations. An Efficient, High-Yield Route to Protected Spirodienones

Shaopeng Wang, Andrew Callinan, and John S. Swenton*

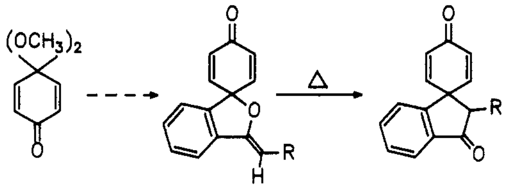
Department of Chemistry, The Ohio State University, 120 West 18th Avenue, Columbus, Ohio 43210

Received February 5, 1990

Summary: Irradiation of ethylene ketals of spiro *p*-quinol vinyl ethers in the presence of piperylene affords protected 2,5-cyclohexadienones in high quantum and chemical yields via a 1,3-oxygen-to-carbon migration.

Many standard methods for carbon–carbon bond formation are not applicable to the construction of quaternary centers in complex organic molecules. The thermal 1,3-oxygen-to-carbon rearrangement of *p*-quinol vinyl ethers is the key step in a carbonyl-to-quaternary carbon transformation described earlier, e.g., 1 → 3.[1] However, selective chemical transformations of the carbonyl groups in 3 could be difficult. In addition, molecules having sensitive functionality may not be stable at the temperature (130–160 °C) required for rearrangement.[1] We report herein that the photochemical 1,3-oxygen-to-carbon migration in these systems at room temperature gives spirocyclic dienone ketals having differentiated carbonyl groups with high chemical and quantum yields.

The photochemistry of the vinyl ether moiety has not been extensively studied. Two primary photochemical processes of ethyl vinyl ether are[2] (1) formation of ethylene and acetaldehyde and (2) formation of ethyl and vinyloxy radicals. No products resulting from a 1,3-oxygen-to-carbon rearrangement were reported.[2] The results from the irradiation of substituted α-(benzyloxy)styrenes with a low-pressure mercury lamp were somewhat more encouraging: β-phenylpropiophenones were formed with quantum yields in the range 0.04–0.11.[3] A triplet excited



1 2 3

---

[1] Wang, S.; Morrow, G. W.; Swenton, J. S. *J. Org. Chem.* **1989**, *54*, 5364–5371.

[2] Murad, E. *J. Am. Chem. Soc.* **1961**, *83*, 1327.

[3] Izawa, Y.; Ogata, Y. *J. Org. Chem.* **1970**, *35*, 3192.

[4] A representative irradiation is described below. These reactions can be performed in either methylene chloride or benzene. Comparable results were obtained in several systems using either a 450-W Hanovia medium-pressure source (Corex filter) or the reactor described below as light sources. A solution of **4b** (1.0 g, 4 mmol) and piperylene (16 mL) in benzene (60 mL) was placed in eight Pyrex test tubes. After nitrogen was bubbled through the tubes for 5 min, they were sealed with a neoprene stopper and irradiated for 2.5 h with 12 RPR-3000 Å lamps in a Rayonet photochemical reactor at room temperature. The combined irradiation mixture was concentrated, and the crude product was filtered through silica gel (1 × 12 cm column, 20% Et_2O/petroleum ether as eluant). The product **5b** (0.97 g, 97%) was obtained as a clear oil, showing spectroscopic properties identical to those reported previously.[1]

0022-3263/90/1955-2272$02.50/0 © 1990 American Chemical Society