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The First Example of a Nitrogen-Substituted Oxyallyl Cation Cycloaddition

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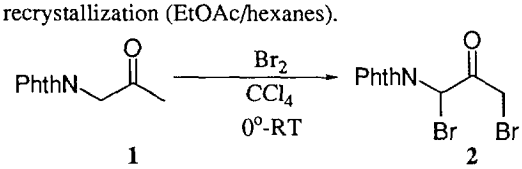
Abstract: The readily available α,α'-phthalimidoyldibromide **2** has been converted to the first reported N-substituted oxyallyl cation by treatment with either CF_3CH_2OH or 3M $LiClO_4$/ Et_2O in the presence of Et_3N. The formation of this reactive intermediate has been demonstrated by its *in situ* cycloaddition with cyclopentadiene and furan.

In the past three decades, the importance of oxyallyl cations in the synthesis of cyclopentanones and bridged-cycloheptanones has been amply demonstrated.[1] This powerful carbon-carbon bond forming process has been used as the key reaction in the synthesis of several important classes of natural products. While carbon- and halogen-stabilized oxyallyl cations have been employed in these studies, the synthetic role of heteroatom-substituted (e. g. S, O) oxyallyl cations has not been as extensively developed.[2]

Notably absent from the realm of heteroatom-stabilized oxyallyl cations are those containing pendant nitrogen substituents. Such species would be attractive reactive intermediates for at least two reasons. First, the potential flexibility to have the nitrogen present in various protected forms could allow the "tuning" of the electron-donating ability of the substituent, perhaps influencing reagent reactivity and selectivity.[3] Second, the trivalent nitrogen atom might provide a means for attaching asymmetric-controlling elements in close proximity to the oxyallyl system.[4] With these potential benefits in mind, we have begun a program to develop useful nitrogen-substituted oxyallyl cations and explore their utility in synthesis. Herein, we report the generation of the first nitrogen substituted oxyallyl cation, and its trapping with several cyclic dienes to form nitrogen functionalized 8-X-bicyclo[3.2.1]oct-6-en-3-ones (X=CH_2, O).

Preparation of α,α'-phthalimidoyldibromide **2** was accomplished as shown in Scheme 1. Employing the method of Gaudry and Marquet,[5] N-acetonylphthalimide **1**[6] was treated with 2 eq of bromine in freshly distilled CCl_4 at RT (room temperature). The known dibromide was isolated as a white solid (mp 125-126 °C, lit.[7] 126-127 °C) in 61% yield after removal of the monobrominated adducts by radial chromatography (30% EtOAc/hexanes) and recrystallization (EtOAc/hexanes).

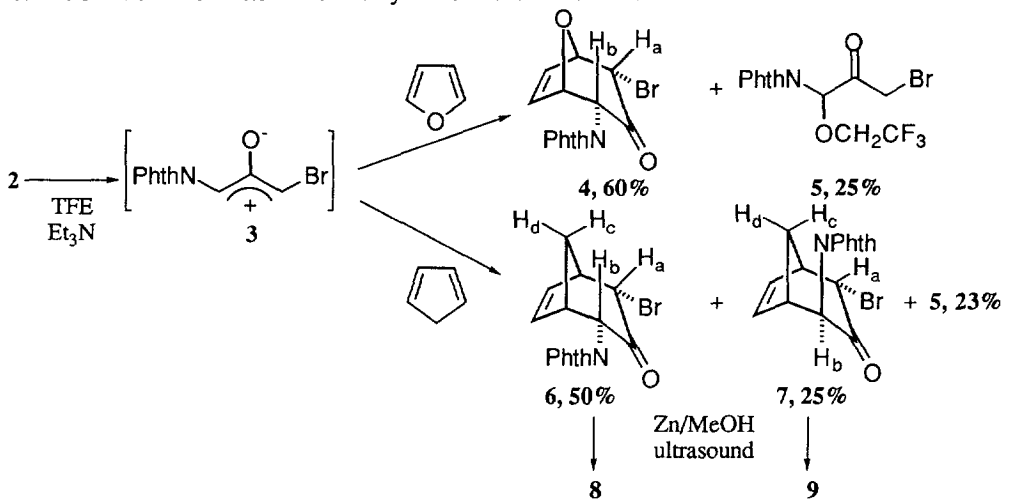


1 **2**

Scheme 1

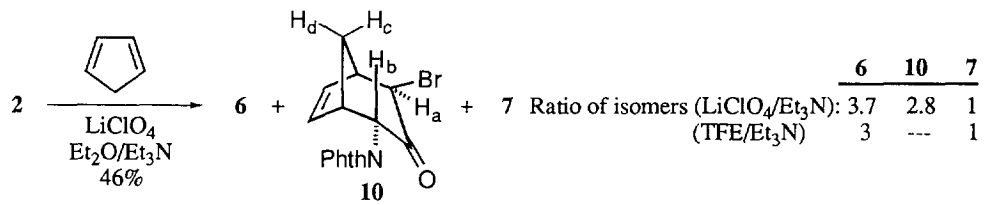
Generation of the nitrogen-substituted oxyallyl cation **3**[8] in the presence of the cyclic dienes cyclopentadiene and furan was accomplished by two known procedures: either by treatement of **2** and the diene with Et_3N in CF_3CH_2OH (TFE)[9] or by addition of the diene to a solution of 3M $LiClO_4$/ Et_2O in the presence of Et_3N.[2c] For example, when **2**, furan, and Et_3N were combined at 0 °C in TFE and allowed to warm to RT over 4 h, a mixture of two products was formed.[10] These products were identified as the cycloadduct **4** (60 %) and solvation product **5** (25 %) (Scheme 2).[11] Separation of the two products using radial chromatography yielded **4** as a white solid which was recrystallized from $CHCl_3$.[12] Using COSY, HETCOR and NOESY 2-D ^{1}H-NMR experiments, we have determined that **4** was formed as a single *endo*-diastereomer, as was anticipated given literature precedence.[13] Consistent with our assignment of **4** as the *endo* isomer, protons H_a and H_b clearly showed a cross peak in the NOESY spectrum, thereby confirming their proximity in space. When cyclopentadiene was used as the diene, both the endo-product **6** (50 %) and

the α,β-product **7** (25 %) were isolated in addition to **5** (23%).[14] Again, NMR experiments were crucial in determining the stereochemistry of the final products. Cycloadduct **6** showed a clear correlation between H_a and H_b in the NOESY spectrum in addition to cross peaks between H_c and H_b and between H_a and H_c. On the other hand, in the NOESY spectrum of bromoketone **7** only H_a and H_c (of the labeled protons) show an NOE interaction. Further confirmation of these stereochemical assignments was accomplished by reductive-debromination of ketones **6** and **7** with Zn/MeOH in an ultrasound bath.[10] As was anticipated, the final products **8** and **9** were diastereomeric only at the N-substituted carbon.



Scheme 2

Formation of oxyallyl cation **3** was also accomplished using conditions reported by Folisch and coworkers.[2c] Unfortunately, lower yields were obtained using these conditions. For example, treatment of dibromide **2** with 3M $LiClO_4$/ Et_2O and Et_3N in furan gave only 15% of cycloadduct **4**. However, trapping of the oxyallyl cation **3** with cyclopentadiene under identical conditions resulted in the formation of **6**, **10**, and **7** in a ratio of 3.7:2.8:1 (46 % yield) (Scheme 3). In this case, the β,α-product **10** was the primary minor isomer formed. The stereochemical assignments were established using 2-D NMR. Additionally, reduction of **10** (*vide supra*) afforded cycloadduct **8**. The α,β-isomers could arise either from the formation of the sickle-configuration of the disubstituted oxyallyl cation, or *via* a non-concerted, stepwise reaction process. The change in cycloadduct isomer ratio observed for the reaction of **3** and cyclopentadiene under different reaction conditons (CF_3CH_2OH/Et_3N or $LiClO_4/Et_3N$) may be rationalized by invoking Li^+ complexation of the phthalimide oxygen and the oxyallyl cation oxygen in the latter case. The Li^+ counterion present in $LiClO_4/Et_3N$ might provide some "chelation-control" of the oxyallyl cation structure, favoring the formation of **10** while diminishing the formation of the cation conformer which would lead to **7**.

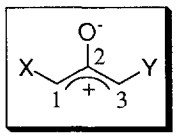


	6	10	7
Ratio of isomers ($LiClO_4/Et_3N$):	3.7	2.8	1
(TFE/Et_3N)	3	---	1

Scheme 3

To enable us to predict the reactivity of the nitrogen-substituted oxyallyl cation reported in this manuscript relative to oxyallyl cations which have already been described in the literature, we have performed semiempirical calculations on three representative oxyallyl cations (**3**, dialkylated **11**, and dibrominated **12**) (Table 1).[15] These calculations suggest that nitrogen-substitution reduces the electrophilicity of the oxyallyl zwitterion (higher LUMO energy relative to furan (HOMO=-9.23225 eV) than in **11** and **12**) while polarizing the LUMO towards nitrogen. The electron-density in **3** is clearly shifted toward the bromine-substituted carbon atom as is evidenced by both the HOMO coefficients and the charge values. Given these results, we predict that nitrogen-substituted oxyallyl cations should be more selective in their reactions than either **11** or **12**,[1c] and that some regioselectivity should be observed in their reactions with unsymmetrically-substituted dienes.

Table 1. HOMO and LUMO Energies, Molecular Orbital Coefficients, and Net Atomic Charges for Three Representative Oxyallyl Zwitterions (PM3).



X	Y		Energy (eV)	C(1)	C(2)	C(3)
PhthN-	Br- (3)	LUMO	-2.23162	-0.65759	0.00691	0.50643
		HOMO	-7.62377	-0.33226	0.17588	0.62920
		Charge		-0.0252	0.2310	-0.2889
CH_3-	CH_3- (11)	LUMO	-2.30273	-0.67780	-0.00391	0.67457
		HOMO	-8.03708	0.52832	0.15880	0.52914
		Charge		-0.0385	0.1892	-0.0387
Br-	Br- (12)	LUMO	-3.09293	-0.67546	0.00001	0.67527
		HOMO	-8.63723	-0.51452	-0.12949	-0.51465
		Charge		-0.1080	0.2005	-0.1081

In conclusion, we have shown that the readily available α,α'-phthalimidoyldibromide **2** is a convenient precursor to the nitrogen-stabilized oxyallyl cation **3**. This stabilized oxyallyl cation reacts quite readily with cyclopentadiene and furan to yield 8-X-bicyclo[3.2.1]oct-6-en-3-ones, where X=CH_2 and O. Semiempirical calculations predict that these new oxyallyl cations should be less electrophilic than comparable symmetrically-substituted cations, and may evince enhanced regioselection with unsymmetrical dienes beacuse of polarization of their LUMOs. Work aimed at evaluating these predictions is underway in our laboratory. Furthermore, since the products of these reactions may be useful precursors to unnatural amino acids and to nitrogen-substituted 5- and 6-membered hetero- and carbocycles, we are investigating the preparation of prochiral oxyallyl cations employing N-linked chiral auxiliaries. Results along these lines of research will be published in due course.

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4. For example, attachment of a chiral oxazolidinone auxiliary might be possible. See: Palomo, C.; Berree, F.; Linden, A.; Villalgordo, J. M. *J. Chem. Soc., Chem. Commun.* **1994**, 1861-1862 and references cited therein..
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8. We have chosen to draw the intermediate **3** as a zwitterion although the true nature of the intermediate in these reactions is probably more complex.
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10. General procedure for cycloaddition using TFE/Et_3N: In a flame dried flask was dissolved 0.200 g (0.709 mmol) phthalimide **2** in 2.8 ml of the appropriate diene and cooled to 0 °C. Subsequently, 1.4 ml TFE and 0.148 ml (0.106 mmol) Et_3N were added to the reaction mixture. The solution was stirred for 4 h while gradually warming to room temperature. The reaction mixure was poured into H_2O and extracted with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Chromatography (25% EtOAc/Hexanes) gave the desired bromoketones as white solids. Separation of the isomers was accomplished using radial chromatrography (25% EtOAc/ Hexanes).
11. All compounds described in this manuscript exhibited characteristic IR, NMR (^{13}C, ^{1}H), and MS. Compounds **4** and **6** gave C and H combustion analysis consistent with their proposed formulae.
12. **4**: mp 170 °C (dec); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.81 (d, 1H, *J* = 4.8 Hz), 5.09 (dd, 1H, *J*= 4.8, 1.7 Hz), 5.23 (dd, 1H, *J* = 4.8, 1.7 Hz), 5.39 (d, 1H, *J* = 4.8 Hz), 6.55 (dd, 1H, *J* = 6.5, 1.5 Hz), 6.61 (dd, 1H, *J*= 6.5, 1.5 Hz), 7.81 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 53.18, 62.60, 81.19, 82.33, 123.68, 131.06, 134.51, 134.83, 135.78, 191.31; Anal. Calcd for $C_{15}H_{10}BrNO_4$: C, 51.75; H, 2.90; N, 4.02. Found: C, 51.70; H, 3.01; N, 3.97.
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14. **6**: mp 187.6-188.1 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.22 (d, 1H, *J* = 12.3 Hz), 2.48 (m, 1H), 3.11 (m, 1H), 3.41 (m, 1H), 4.85 (d, 1H, *J* = 3.6 Hz), 5.15 (d, 1H, *J* = 3 Hz), 6.29 (dd, 1H, *J* = 5.4, 2.7), 6.42 (dd, 1H, *J* = 5.4, 2.7 Hz), 7.80 (m, 4H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 43.92, 45.60, 48.76, 57.64, 63.29, 123.74, 133.35, 134.32, 134.63, 138.09, 194.47; MS m/z (relative intensity) 347(M+, 10), 348(M+2, 3), 279 (12), 167(31), 149(100), 71(23), 70(22), 57(44), 55(18); Anal. Calcd for $C_{16}H_{12}BrNO_3$: C, 55.51; H, 3.49; N, 4.05. Found: C, 55.21; H, 3.39; N, 3.99
15. A planar geometry was assumed for each of the oxyallyl species in order to simplify the determination of the molecular orbital coefficients. This planar geometry was an energy minimum for **11** and **12**. Species **3** adopts a slightly skewed geometry (PhthN- out of plane) in its minimum conformation. The planar conformation used here was 1.17 kcals/mol (8%) higher in energy than the skewed conformation. The same ordering of LUMO energies was found if the O-protonated form was employed rather than the zwitterionic structures **3**, **11**, and **12**. Calculations were performed using MOPAC. Stewart, J. J. P. *MOPAC, ver. 6.0*; Serena Software, Box 3076, Bloomington, IN 47402.

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