AMINO- AND THIOMETHYLENATION OF MALEIMIDES

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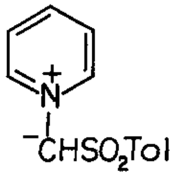
Abstract Reaction of pyridinium p-toluenesulfonylmethylide with N-substituted maleimides in the presence of primary or secondary amines gives aminomethylenesuccinimides (**4**). The geometry of these enamines is presented. In one case, the E- and Z-isomers have been separated and characterized. The NMR spectra of the geometrical isomers is discussed. When thiophenol is used as the nucleophile a small yield of the phenylthiomethylenesuccinimide is obtained, but nucleophilic addition of the thiol to the maleimide takes place.

Pyridinium p-toluenesulfonylmethylide (**1**) has recently found application as a formyl anion equivalent and, in the presence of an alcohol or a phenol, was shown to undergo 1,4-addition to N-substituted maleimides (**2**) to give alkoxy- (or aryloxy)-methylenesuccinimides (**3**).[1] When R' = $CH_2C_6H_4$-p-OMe the protected aldehyde group could be readily cleaved with HBr in CH_2Cl_2 at room temperature to liberate the formyl group.



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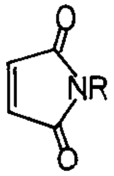

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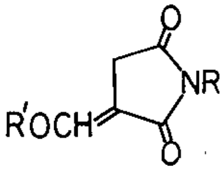

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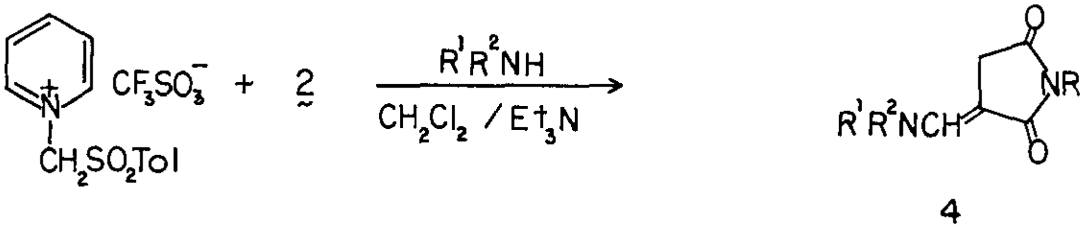
Since the mechanism of the formation of **3** undoubtedly involves nucleophilic displacement by R'OH of the pyridinium ion from an intermediate adduct it seemed likely that other nucleophiles could function similarly. We now report the use of primary and secondary amines and of thiols for this purpose.

The results with amines were reasonable and are summarized in Table I. The yield of enamine **4** ranged from 77.5% for piperidine to zero with o-nitroaniline and acetanilide. The structures of the enamines were confirmed on the basis of their spectral properties. Two carbonyl stretching bands were observed at 1740-1725 and 1690-1660 cm^{-1}, respectively, the latter clearly indicating that one of the carbonyl groups was in conjugation with the olefin. With primary amines, ν_{NH} was observed as a weak band in the range 3280-3250 cm^{-1}. The olefin bond gives rise to a strong band in the range 1660-1590 cm^{-1} and is at a lower frequency than the enol ether counterpart, consistent with stronger delocalization of the non-bonded electron pair in the enamines than in the enol ethers. The vinyl proton gave rise to a triplet and the ring CH_2 group to a doublet (Table II) and the small coupling (∼2 Hz) is in accord with the allylic relationship of these groups.

In two cases in which primary amines were used (R_1 = *n*-Pr; R_2 = H and R_1 = Ph; R_2 = H) TLC indicated that a mixture of two products was formed. These were shown to be geometrical isomers by NMR analysis. In the case of the *n*-proplyamino derivative, isolation of the individual TLC fractions followed by redissolution in $CDCl_3$ gave rise to the same mixture of the two compounds from each of the individual enamines. In the case of the anilino derivative the two isomers were stable enough to be individually analyzed and their spectral properties determined. The isomer mp 178°C is assigned the *E*-geometry (RNH relative to adjacent amide C=O) and the one mp 123°C the *Z*-geometry (**6**). Table II contains a comparison of the chemical shifts for the vinyl protons and calculated values.[2-4] The observed δ values are, in some cases, higher than calculated (the values of R used are probably imprecise) but are in good agreement with those for other enaminocarbonyl compounds.[5] The downfield shift of the vinyl proton in the *E*-form (**5**) relative to that in the in the *Z*-form (**6**) is undoubtedly owing (at least in large measure) to deshielding by the adjacent carbonyl in the same plane. In the case of **4** (R = Me, R^1 = *n*-Pr, R^2 = H) the NMR absorptions for both isomers [δ 7.28 (*E*), 6.53 (*Z*)] were observed in solution. In all the other cases only one peak was observed, suggesting the equilibration was fast with respect to the NMR time scale. Indeed, no separation on TLC could be effected. Comparison with the spectra of the above compounds suggests that the aliphatic amines give mainly the *E*-isomer while aromatic ones give mainly the *Z*. It is tempting to speculate that the predominant geometry of the final product is determined by dipolar repulsions (or attractions) between the carbonyl group and the amine (repulsion with aliphatic, attraction with aromatic).

Analysis of the spectra of the enol ethers (**3**) (R = Me, Ph, 3-Cl-4-FC_6H_3, or *p*-MeO$CH_2C_6H_4$; R^1 = Et) indicates that they all exist (at least predominantly) in the *E*-form.[6] The use of thiols as nucleophiles was successful in only one of the cases we studied. Reaction of **1** with **2** in the presence of thiophenol gave a low yield (5%) of **7**, mp 139-140°C, and *N*-phenyl-3-phenylthiosuccinimide (**8**), mp 145°C, together with *N*-phenyl-3-*p*-toluenesulfonylsuccinimide (18%). 4-Methoxybenzenethiol gave only *N*-phenyl-3-(*p*-methoxyphenylthio)succinimide (90%). It would seem that using less nucleophilic thiols will be required to avoid this important side-reaction. Compound **7** is a mixture of both *E*- (δ 7.78, t) and *Z*-forms (δ 7.20, t) in solution.

Table I. Formation of Aminomethylenesuccinimides.



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Amine	R	Yield of 4 (4%)	mp (°C)
$\underline{n}$-$C_3H_7NH_2$	CH_3	74.7	120-121
Piperidine	CH_3	77.5	142-142.5
$PhNH_2$	CH_3	39.7	124.5-125
$PhNH_2$	Ph	38 ($\underline{Z}$) 20 ($\underline{E}$)	123 178
$\underline{m}$-$BrC_6H_4NH_2$	Ph	35	158.5-159
$PhNHCH_3$	Ph	28	150
Piperidine	Ph	39	147.5-148
Morpholine	Ph	43	148.5-149
$C_6F_5NH_2$	Ph	32.8	[a]
$\underline{o}$-$NO_2C_6H_4NH_2$	Ph	0	
$PhNHCOCH_3$	Ph	0	

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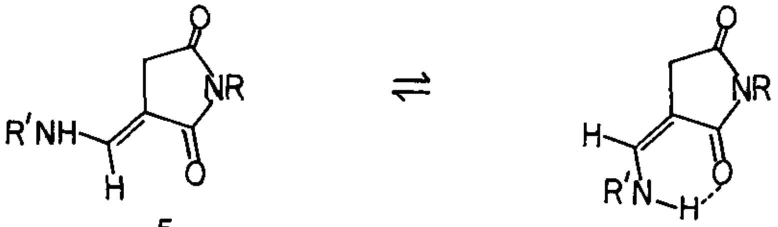
[a] Analytically pure sample was not obtained.



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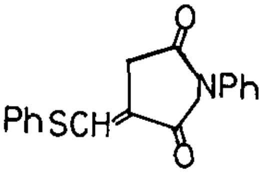

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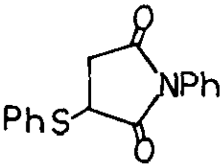

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Table II. NMR Spectra of Aminomethylenesuccinimides (**4**).

R	R^1	R^2	δ (ppm) Vinyl H	δ (ppm) Ring CH_2	Calcd. $\delta_{vinyl\ H}$ E	Calcd. $\delta_{vinyl\ H}$ Z
Me	*n*-Pr	H	7.28 (t) (*J* = 1.5 Hz)	3.08		
			6.53 (t)	3.08 (d)		
Me	$-C_5H_{10}-$		7.50 (t) (*J* = 2.0 Hz)	3.46 (d)	6.60	5.99
Ph	$-C_5H_{10}-$		7.41 (t) (*J* = 1.4 Hz)	3.50 (d)		
Ph	$-(CH_2)_2NH(CH_2)_2-$		7.43 (t) (*J* = 1.3 Hz)	3.50 (d)		
Ph	Ph	H	8.05 (t)[a] (*J* = 2.5 Hz)	3.44 (d)		
			7.05 (t)[b] (*J* = 1.5 Hz)		8.21	7.60
Ph	Ph	CH_3	7.67 (t) (*J* = 1.5 Hz)	3.15 (d)		
Ph	*m*-BrC_6H_4	H	7.22 (t) (*J* = 2Hz)	3.50 (d)		

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[a] Isomer mp 178°C. [b] Isomer mp 123°C.

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REFERENCES AND NOTES

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2. L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," (2nd Edn.), Pergamon Press, Oxford, **1972**, p. 185.
3. J. Dabrowski and K Kamienska-Trela, Spectrochim. Acta **1966**, **22**, 211.
4. The calculations were made using equation

$$\delta_{vinyl\ H} = 5.28 + \sum_i Z_i$$

$$\text{when } \Sigma Z_i = R_{gem} + R_{cis} + R_{trans}$$

using R_{gem} = 1.18 (OAlk), 1.00 (SR), 0.69 (NR^1R^2), 2.30 (NRAr)

R_{cis} = 0.93 (N-C=O), -0.33 (CH_2) (ring); R_{trans} = 0.35 (N-C=O), -0.30 (CH_2) (ring)

5. R. Huisgen, K. Herbig, A. Siegl, and H. Huber, Chem. Ber. **1966**, **99**, 2526.
6. Found: $\delta_{vinyl\ H}$ = 7.76 - 7.72. Calcd.:[2-4] δ_E = 7.09; δ_Z = 6.48.

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