REACTIVITY OF 2-MORPHOLINOBUTADIENES WITH HETEROCUMULENES: STEREOSELECTIVE SYNTHESIS OF THINS AND NEW 2-MORPHOLINOBUTADIENE DERIVATIVES

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Summary: 2-Morpholinobutadienes have been found to show different behaviour in the reaction with isocyanates and isothiocyanates. While isocyanates give rise always to open chain compounds, isothiocyanates yield mainly thin¹ derivatives.

In previous papers² we have reported the reactivity of the readily available 2-morpholinobutadienes³ with a wide variety of dienophiles showing an enamine behaviour, except in those cases where a substituent of the aminodiene could participate in the reaction. Furthermore, the high regio- and stereoselectivity observed made 2-morpholinobutadienes interesting starting materials for the preparation of highly functionalized compounds.

Continuing with this work and due to our interest in the Diels-Alder reaction,⁴ we decided to extend the study of the behaviour of 2-aminodienes towards other types of dienophiles, such as isocyanates and isothiocyanates in order to prepare modified 2-aminobutadienes.

It is worth noting that isocyanates and isothiocyanates react readily with enamines affording addition or substitution products.⁵ However, as much as we know, there are no examples of the reaction of a cross-conjugated enamine with isothiocyanates in the literature and only one involving isocyanates, which leads to a mixture of Z, E-diastereoisomers, has been described.⁶

The treatment of 2-morpholinobutadienes 1 with one equivalent of isocyanates 2 (X=O), in dry THF (25°C, 6 h), afforded new substituted 2-morpholinobutadienes 47 in an almost quantitative yield as single diastereoisomers, as detected by NMR spectra of the reaction crude (*Scheme I*)(*Table I*). The acid hydrolysis (1N•HCl, 25°C, 2 h) of 4 led to the corresponding β -oxoacid derivatives 6.8

On the other hand, treatment of 2-morpholinobutadiene 1 ($\mathbb{R}^3=\mathbb{H}$) with isothiocyanates 2 (X=S) in the same reaction conditions as above, afforded cycloadducts 5 as single diastereoisomers⁹ (*Scheme I*)(*Table I*). When $\mathbb{R}^3\neq\mathbb{H}$ cycloadduct 5 was not obtained, but the reaction afforded a complex reaction mixture, from which the thiourea derived from the addition of morpholine to the isothiocyanate was identified. Compounds 5 could not be hydrolyzed in the same reaction conditions as 4 but their hydrochloride salts were isolated as crystalline substances.



Table I. New morpholinobutadienes 4 and aminothiin derivatives 5 prepared

Compound	R1	R2	R ³	Ar	m.p.b °C	Yield ^a %
4a	CH3	CH ₂ OCH ₃	н	p -Tol	109	98
4b	CH3	CH ₂ OSi(CH ₃)	3 H	p -Tol	112	96
4c	CH3	Н	CH ₂ OCH ₃	<i>p</i> -Tol	172	97
4d	-((CH2)4-	н	p -Tol	209	99
4 e	CH3	CH ₂ OCH ₃	Н	Ph	112	98
5a	CH3	CH ₂ OCH ₃	Н	Ph	157	96
5b	CH3	CH ₂ OSi(CH ₃)	3 H	Ph	178	96
5 c	-(CH ₂)4-		Н	Ph	152	92
5d	CH3	Н	Н	Ph	Oil	89
5e	CH3	CH ₂ OCH ₃	Н	p-Cl-Ph	130	98

a) Yield of the crude reaction product. All the new compounds were characterized by high resolution NMR analysis.¹⁰ b) Melting points are uncorrected.

The stereochemical assignment of compounds 4 was based on steady-state NOE experiments carried out on 4e as a model. Saturation of H_a by low power irradiation causes positive NOEs at H_b (4 %), and H_c (11 %), establishing the *E* configuration of the enaminic double bond as well as the preferred conformation of the amidic moiety (*Scheme I*) imposed

by the restricted rotation around the C-N bond. Moreover, when the saturation of R^1 (=Me) takes place, positive NOEs are observed for the methylene protons in R^2 (10%) and for Hb (3%), which in turn afford an indirect NOE on H_a (-8%). This clearly shows that compounds 4 exist in solution in the (*s*-*cis*) - conformation showed in *scheme I*.

The relative configuration of aminothiin derivatives 5 at C₅ and C₆ was determined through the analysis of the coupling patterns of H₅ and H₆ in the ¹H-nmr spectrum and confirmed by a NOESY experiment carried out in the phase sensitive mode.¹¹ Thus, H₅ shows a very small vicinal coupling to H₆ (H₅, dq, ${}^{3}J_{H5-CH3} = 6.9$ Hz, ${}^{3}J_{H5-H6} = 2.9$ Hz) and no cross-peaks were found between H₆ and R¹ (=Me) in the NOESY spectrum, pointing to a *syn* arrangement of the substituents R¹ and R² in the molecule. Otherwise, difference spectroscopy also showed that the *trans*- configuration of the enaminic double bond was again retained in 4c. But, instead a preference for the *s*-trans conformation of the dienic system was found. Saturation of the high field multiplet of the morpholino substituent produces positive NOEs at the methylene protons of R³ (2 %) and at H_a (14 %).

The formation of adducts 4 and 5 can be understood by a step-wise reaction. Thus, nucleophilic attack of C β -enamine carbon atom to the electrophilic center of the heterocumulene followed by either intramolecular cyclization (X=S) or proton abstraction (X=O) can explain the process. The different behaviour of isocyanates and isothiocyanates can be rationalized in terms of the higher nucleophilic character of sulphur along with the higher basicity of the oxygen atom. (Scheme II).



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References and notes

- 1.- The systematic name for a six membered ring containing one sulphur atom is thiin, but *Chemical Abstracts* uses the name thiopyran, so both terms can be used interchangeably.
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- 4.- J. Barluenga, M. Tomás, A. Ballesteros, L.A. López. Tetrahedron Lett., 1989, 30, 6923, and references cited therein.
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- 7.- Spectroscopic data *e.g.* 4a ¹H NMR (CDCl₃) 300 MHz δ = 7.35 (d, 2H), 7.25 (m, 1H), 7.05 (d, 2H), 5.63 (t, 1H), 4.77 (s, 1H), 4.05 (d, 2H), 3.76 (t, 4H), 3.32 (s, 3H), 3.06 (t, 4H), 2.23 (s, 3H), 1.92 (s, 3H) ppm. ¹³C NMR (CDCl₃) 75 MHz δ = 165.69 (s), 161.77 (s), 136.41 (d), 132.99 (s), 132.60 (s), 131.99 (s), 120.20 (d), 119.50 (d), 94.47 (d), 69.10 (t), 66.43 (t), 59.1 (q), 47.4 (t), 20.7 (q), 17.1 (q) ppm. MS (m/e): 330 M⁺.
- 8.- Spectroscopic data e.g. 6a ¹H NMR (CDCl₃) 300 MHz δ= 9.16 (s, 1H), 7.42 (d, 2H), 7.19 (d, 2H), 6.83 (m,1H), 4.23 (d, 2H), 3.82 (s, 2H), 3.40 (s, 3H), 2.26 (s, 3H), 1.76 (s, 3H). ¹³C NMR (CDCl₃) 75 MHz δ= 195.56 (s), 164.91 (s), 141.08 (d), 136.48 (s), 134.01 (s), 133.35 (s), 128.78 (d), 119.80 (d), 69.10 (t), 58.06 (q), 45.13 (t), 20.30 (q), 11.00 (q).
- 9.-Spectroscopic data *e.g.* 5a ¹H NMR (CDCl₃) 300 MHz δ = 7.31 (m, 2H), 7.07 (m, 1H), 6.92 (m, 2H), 5.60 (s, 1H), 3.75 (m, 5H), 3.41 (dd, 1H, J_{gem} =10.8 Hz., $J_{\alpha-H6}$ =10.4 Hz), 3.23 (dd, 1H, J_{gem} =10.8 Hz., $J_{\beta-H6}$ =6.0 Hz), 3.27 (s, 3H), 3.16 (m, 4H), 2.87 (dq, 1H, J_{H5-CH3} =6.9 Hz, J_{H5-H6} =2.9 Hz), 1.12 (d, 3H, J_{H5-CH3} =6.9 Hz) ppm.¹³C NMR (CDCl₃) 75 MHz δ = 161.73 (s), 160.35 (s), 151.1 (s), 128.6 (d), 123.44 (d), 120.75 (d), 99.82 (d), 71.28 (t), 66.26 (t), 58.88 (q), 46.74 (t), 44.58 (d), 30.28 (d), 11.06 (q) ppm.
- Performed on a Brüker AC 300. The frecuencies for the proton and carbon 13 nuclei were 300 MHz and 75 MHz respectively.
- 11.- The standard three pulses NOESYPH sequence applied with the Bruker software was used.

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