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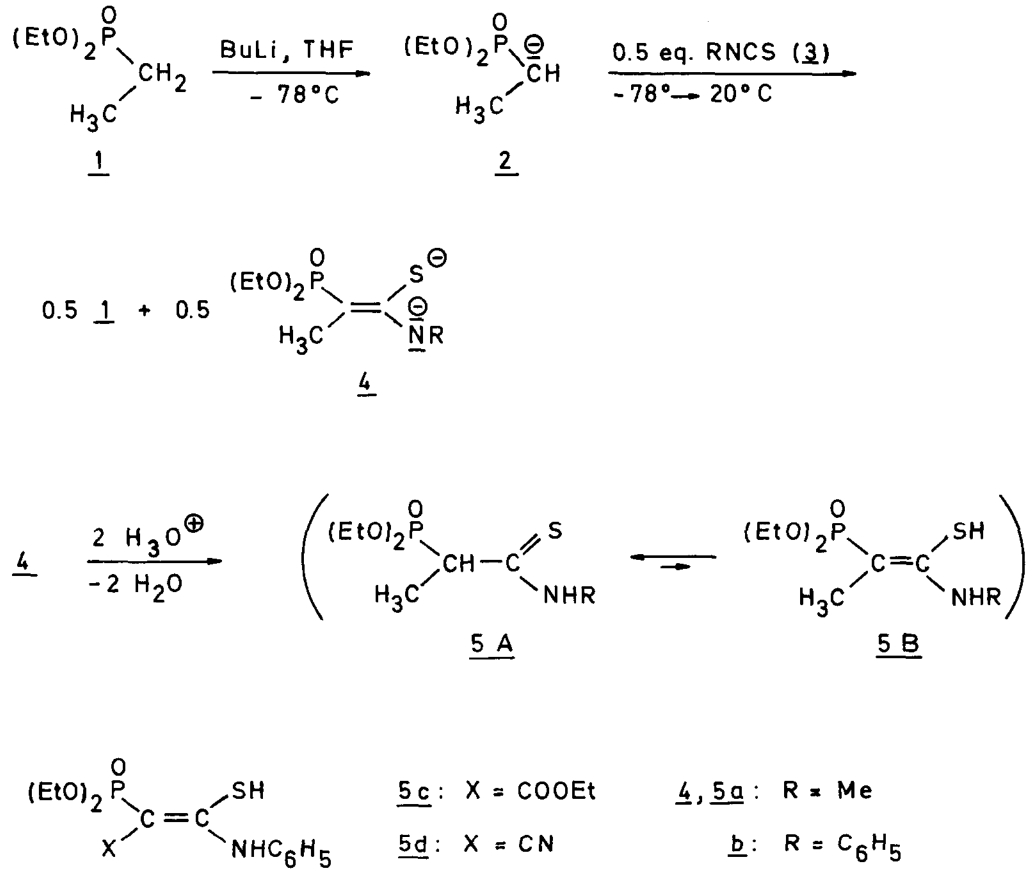
α,β-UNSATURATED THIOAMIDES VIA WITTIG-HORNER OLEFINATION

Ernst Schaumann* and Stefan Fittkau
Institut für Organische Chemie, Universität Hamburg,
Martin-Luther-King-Platz 6, D-2000 Hamburg 13, W. Germany

Summary - Reaction of phosphonate carbanions 6 with aromatic or α,β-unsaturated aldehydes 7 provides facile access to the title compounds 8.

Because of its versatility, the thioamide group plays an important role in synthetic methodology[1]. α,β-Unsaturated secondary thioamides are of particular interest as Michael acceptors[2]; after N-silylation, they add a broad range of organometallics in a 1,4-fashion[2] thus surpassing the corresponding amides[3]. Unfortunately, the conventional method for thioamide synthesis, i. e. thionation of the corresponding amide by the action of some phosphorus sulfide, fails for α,β-unsaturated secondary thioamides due to polymerization[2,4] or in situ addition of hydrogen sulfide[5]. A possible synthesis of the title compounds involves addition of isothiocyanates to olefinic organometallics or to allylmagnesium bromide followed by a base-catalyzed shift of the C=C bond[2]. However, these approaches are limited to examples with alkyl groups on the C=C bond. Another route to α-unsubstituted α,β-unsaturated secondary thioamides is via a Wittig reaction[6]. Finally, insertion of alkynyl silyl sulfides into C=N bonds provides access to unsaturated thioamides[7].

Considering the broad applicability of the Wittig-Horner olefination[8], α-phosphono thioamides 5 should be precursors of the title compounds 8. Thioamides 5a,b can be obtained via addition of carbanions 2 to methyl (3a) or phenyl isothiocyanate (3b). Since in the primary adduct the α-position is more acidic than in 1, a dianion 4 results and only 50% of 2 can be converted into the desired addition product. However, due to their acidity, compounds 5a,b can be easily separated from starting-material 1 by extraction of the reaction mixture with aqueous sodium hydroxide. Thus, based on converted 1, good yields of 5a[9] [50%; oil; ir (film) 3220 (NH), 1240-1200 (P=O), 1060-1000, 950 (POC), 820, 790 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ = 1.33 (t, J = 7 Hz; 6H, POCMe), 1.54 (dd, $^3J_{HP}$ = 20 Hz, $^3J_{HH}$ = 7 Hz; 3H, PCMe), 3.16 (dd, ^3J = 5 Hz, $^5J_{HP}$ = 2 Hz; 3H, NMe), 3.53 (dq, $^3J_{HH}$ = 7 Hz, $^2J_{HP}$ = 21 Hz; 1H, PCH), 3.8-4.4 ppm (m; 4H, $POCH_2$)] and 5b[9] [87%; m.p. 104-106°C (ethyl acetate/petroleum ether); ir (KBr) 3350/3300 (NH), 1210/1190 (P=O), 1040-1010, 960 cm^{-1} (POC); ^{1}H nmr ($CDCl_3$) 1.30 (t, $^3J_{HH}$ = 7 Hz; 6H, POCMe), 1.63 (dd, $^3J_{HP}$ = 18 Hz, $^3J_{HH}$ = 7.4 Hz; 3H, PCMe), 3.65 (dq, $^2J_{HP}$ = 21.6 Hz, $^3J_{HH}$ = 7.4 Hz; 1H, PCH), 3.5-4.5 (m; 4H, $POCH_2$), 7.1-8.0 (m; 10H, aryl-H), 11.1 ppm (broad s; 1H, NH); ^{13}C-nmr ($CDCl_3$) δ = 198.0 (d, $^2J_{CP}$ = 7 Hz; C=S), 139.3, 129.7, 126.5, 123.2 (aryl-C), 63.7-62.9 (OCH_2), 49.6 (d, $^1J_{CP}$ = 126 Hz; P-C), 16.5-15.8 ppm (POC$\underline{C}$, PC$\underline{C}$)] are obtained. The spectroscopic evidence shows that, within instrumental limitations, 5a,b exist in the thioamide form 5A exclusively and not in the ketene S,N-acetal form 5B. This is in contrast to the previously reported compounds 5c,d, where the electron-withdrawing groups X increase CH acidity and for which, consequently, the configuration B of heterosubstituted vinyl phosphonates has been established[10].

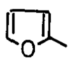


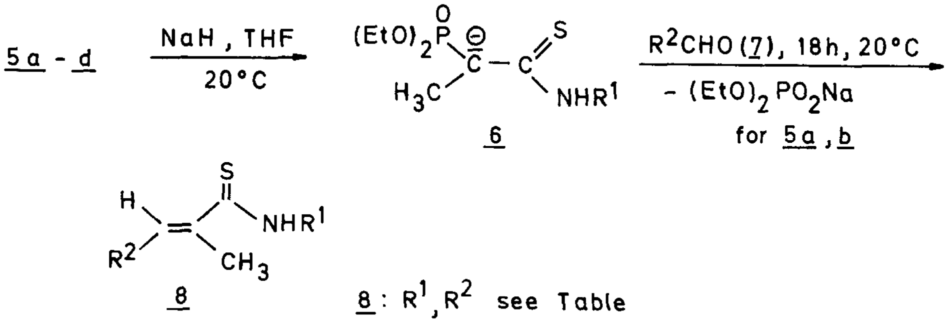
5c: X = COOEt   4, 5a: R = Me

5d: X = CN   b: R = C_6H_5

Addition of an equimolar amount of sodium hydride in THF at 20°C to thioamides 5a-d results in hydrogen evolution indicating formation of anions 6. Starting from 5c,d, no olefination of added benzaldehyde could be achieved (8 h, 65°C). However, anions 5a,b give a smooth reaction with aromatic aldehydes or cinnamaldehyde at room temperature to yield yellow α,β-unsaturated secondary thioamides 8 (Table). As expected, benzaldehyde gives a better yield than more electron-rich aldehydes. In contrast to these results, no reaction could be achieved with aliphatic aldehydes (7 with R^2 = iPr or Bu) or with acetophenone. Thus, the method is limited to the synthesis of thioamides with aromatic or unsaturated groups R^2, but it nicely complements the reported approach[2] to compounds 8 with aliphatic groups R^2.

Table. Yields and characteristic data for the new unsaturated thioamides 8[9]

	R^1	R^2	yield [%]	m.p. [%]	spectroscopic data (solvents: for ir spectra KBr or neat, for ^1H nmr measurements $CDCl_3$)				
					ν_{NH}	$\nu_{C=C}$	$\nu_{thioamide}$	$\delta_{=CCH_3}$	($^4J_{HH}$[Hz])
8a	Ph	Ph	89	70(dec.)	3200	1590	1520, 1490	2.23	(1.2)
8b	Me	Ph	40	66	3300	1620	1525	2.23	(1.2)
8c	Ph	4-MeC_6H_4	47	103-104	3150	1590	1525, 1490	2.25	(0.9)
8d	Me	4-MeC_6H_4	39	oil	3270		1520, 1505	2.18	(1.3)
								2.05	(1.5)
8e	Ph	4-$MeOC_6H_4$	33	87-88	3160	1600	1505, 1495	2.23	(1.2)
8f	Ph	2,4-$(MeO)_2C_6H_3$	17	121-122	3250	1600	1500	2.28	(1.5)
8g	Ph	4-$Me_2NC_6H_4$	50	70-71(dec.)	3250	1600	1520, 1495	2.36	(1.1)
8h	Ph		82	81	3200	1590	1490	2.28	(1.0)
8i	Ph	Ph-CH=CH-	48	121	3300	1605	1500, 1495	2.21	(?)
						1585			



Products 8 are isolated as pure diastereomers. Distinction between the E/Z isomers should be possible based on the position of the HC=C signal in the ^1H nmr spectrum. However, a corresponding signal can only be detected in the spectrum of 8h (δ = 7.01 ppm); in the spectra of 8a-g,i the resonance is obscured by the absorption of the aromatic protons. A range of δ = 6.7-8.0 ppm seems reasonable for E-8. These values are comparable to the signal positions in α,β-unsaturated E-esters, whereas the olefinic proton in the Z-esters absorbs in the range of δ = 5.35-5.85 ppm[11]. Interestingly, chromatographic purification of 8d leads to formation of a second isomer in which the olefinic proton is shifted to higher field [$\delta_{=CH}$= 6.08 ppm (broad s)] indicating Z geometry. Integration of the ^1H nmr spectrum gives Z:E=82:18. Positions and $^4J_{HH}$ couplings of the allylic methyl groups are less helpful in configuration assignment (Table).

Formation of unsaturated thioamides 8 marks the first successful Wittig-Horner olefination employing phosphonates with a β-thioxo group. Attempts to use α-phosphono dithiocarboxylates for C=C bond formation failed probably due to reduced nucleophilicity of the α-position in the anions corresponding to 6 (with SR instead of NHR^1)[12]. It should be noted, however, that the use of 5 is also influenced by the nature of the third substituent on the α-carbon as indicated by the failure of the attempted olefinations with 5c,d. Obviously, three electron-withdrawing groups on the α-carbon in 6 do not provide the electron density required for attack on the electrophilic aldehydes.

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