REACTIVITY OF CONJUGATED ENAMINOTHIOAMIDES TOWARD ACTIVATED ACETYLENIC COMPOUNDS

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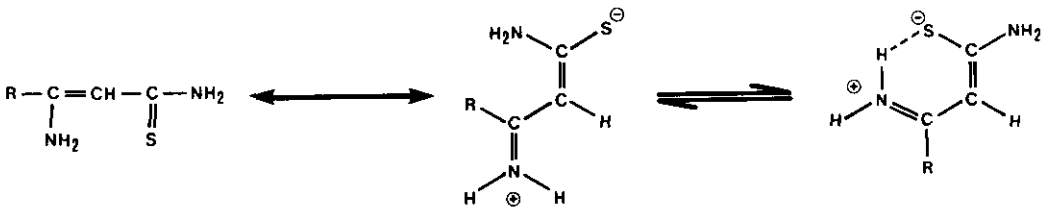
Abstract - Conjugated enaminothioamides react in high-yield with acetylenedicarboxylic acid or its ester derivatives to give 2-enaminothiazolin-4-ones. A similar reaction is observed with propiolic acid and derivatives, giving 2-enamino-1,3-thiazin-4-ones. A substituted thiazoline is quantitatively obtained from propargyl bromide.

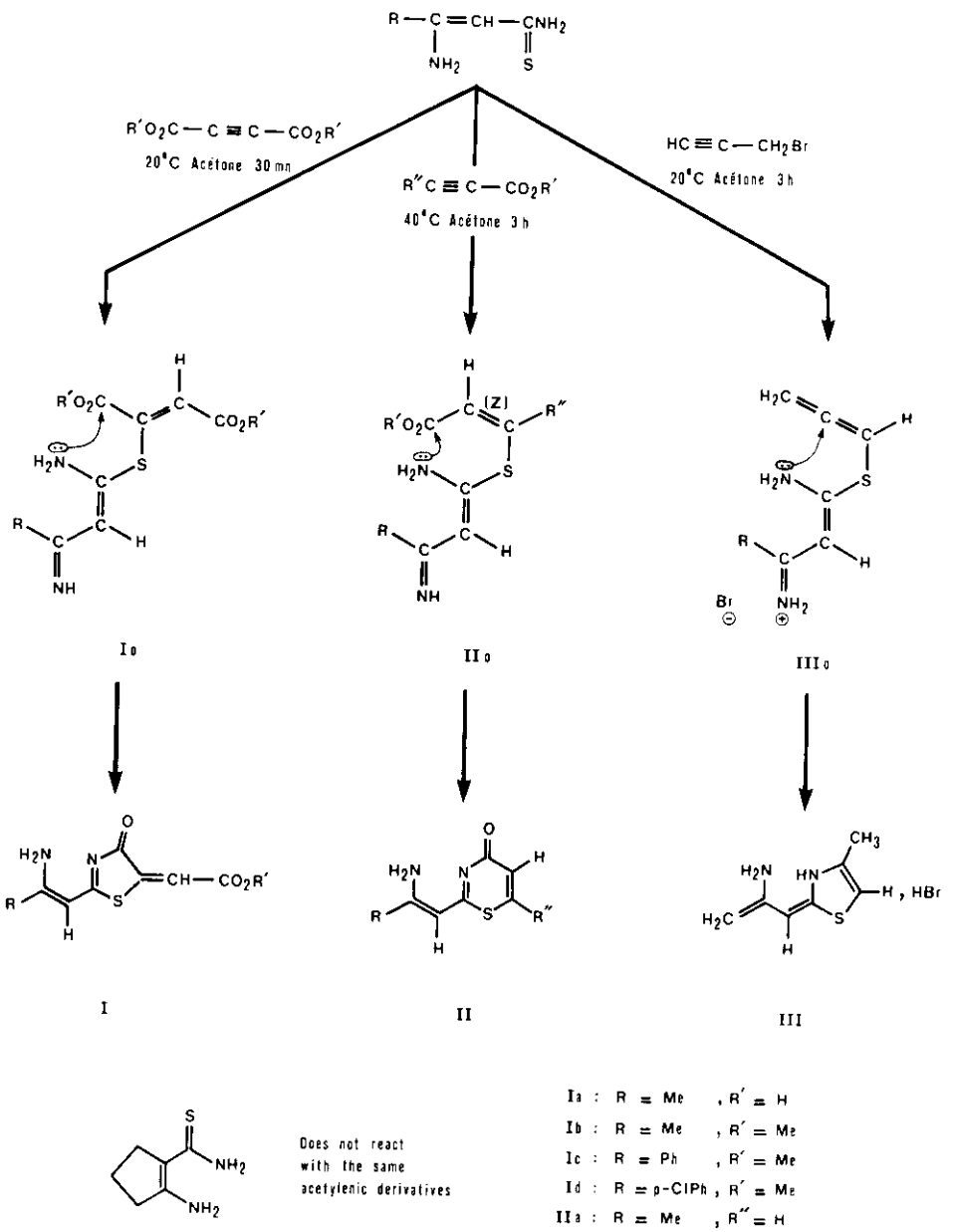
Many works concerning the chemistry of thiourea have shown that this compound could condense with various substrates, particularly with activated acetylenic derivatives[1-2] . It seemed interesting to verify the conjugated enaminothioamides showed an analogous reactivity, since the strong electron-donating enamino group induces in these molecules a dipolar structure, increasing the nucleophilic power of the sulphur atom as in thiourea.[3]

Therefore we allowed to react with acetylenic acids, its ester derivatives and propargyl bromide some enaminothioamides previously synthetized in our laboratory.[4] Under mild conditions, the formation of heterocyclic compounds is observed if the enaminothioamide could exist under a transoïd iminium conformation. Such a conformation allows a higher negative charge on the sulphur atom (scheme 1). When the enaminothioamide does not exist but under a frozen cisoïd iminium conformation, no reactivity is observed. Effectively, 2-aminocyclopentenylthioamides do not react under similar experimental conditions.



Scheme 1

Moreover, if the electron-donating character of the enamino nitrogen is decreased by the presence of an electron-withdrawing group on the chain, we notice a lower reactivity of the thioamide. The formed products are described in scheme 2.



Scheme 2

The first step of these reactions consists in a nucleophilic attack of the sulphur atom, the formed adducts (I_o, II_o, III_o) leading to the three classes of compounds obtained. The intermediates (II_o) were identified (VPC/MS) under their uncyclizable (E) configuration.

I_o and II_o result from a Michael addition on a conjugated triple bond. As for III_o, it is well known that some nucleophilic substitutions on propargylic derivatives yield allenic products quantitatively[5-6]. The electron-withdrawing character of imine and iminium groups involves a nitrogen attack on the β to the sulphur carbonyl group (I_o), or on the central allenic carbon[7] (III_o). Furthermore, the δ to nitrogen electrophilic center is conveniently located for ring closure via the amino group, and no competitive reactivity is observed. When such an electrophilic position lacks (II_o), cyclisation occurs at the less reactive ε to nitrogen position, yielding a six-membered heterocycle.

The nature of the formed compounds shows that thiourea and the studied enaminothioamides display identical reactivities toward acetylenic derivatives[8] . Contrarily to the general behaviour of enamines[9] , the enamino group does not directly participate to the described reactions, but strongly activates the thioamide group.

EXPERIMENTAL

Elementary analyses were performed by the microanalytical service of St-Jérôme, Marseille. Infrared spectra were run on a Perkin-Elmer 457 Spectrophotometer. Nmr spectra were recorded on a Bruker CW 80 at 80 MHz ; mass spectra on an A.E.I. model MS 50. All syntheses were carried out using stoichiometric amounts of reagents stirred in anhydrous acetone. The formed products were recrystallized from an acetone-water mixture.

2-(2-Aminopropenylidene)-5-carboxymethylenethiazolin-4-one (compound Ia)
Yield 90% ; m p 255°C; ir (KBr) : 3205, 3080 (N-H) ; 1670 (C=O acid) ; 1705 (C=O). ^{1}H-nmr (DMSO-D_6) : 10.15 (s, NH), 9.55 (s, NH), 6.62 (s, 1H, C=CH), 5.31 (s, 1H, C=CH), 2.20 (s, CH_3). ^{13}C-nmr (DMSO, D_6) : 180.03; 177.66 ; 169.92 ; 167.64 ; 145.79 ; 116.74 (=CH) ; 92.53 (=CH) ; 21.85 (C-CH_3). Mass spectrum, m/e(70 ev, relative intensity), 213 (M^+, 17), 212 (100), 168 (11), 102 (10.2), 86 (15.8), 85 (11), 84 (100), 83 (100), 67 (17), 58 (15.5), 42 (43.7).

2-(2-Aminopropenylidene)-5-carbomethoxymethylenethiazolin-4-one (compound Ib)
Yield 95% ; mp 280°C; ir (KBr) : 3210, 3080 (N-H) ; 1685 (C=O ester) ; 1705 (C=O). ^{1}H-nmr (DMSO-D_6) : 10.20 (s, NH), 9.65 (s, NH), 6.62 (s, C=CH), 5.34 (s, C=CH), 3.76 (s, CO_2CH_3), 2.20 (s, CH_3). ^{13}C-nmr (DMSO-D_6) : 179 ; 175.50 ; 170.22 ; 166.35 ; 146.96 ; 113.65 (=CH) ; 92.70 (=CH) ; 52.00 (O-CH_3) ; 21.84 (C-CH_3). Mass spectrum, m/e(70ev, relative intensity), 226 (100), 167 (14.5), 145 (14.6), 144 (32.3), 116 (32.3), 85 (45.8) 83 (39.6), 82 (100), 67 (29), 42 (45.8).

2-(2-Amino-2-phenylethylidène)-5-carbomethoxymethylenethiazolin-4-one (compound Ic)
Yield 30% ; m p 256°C ; ir (KBr) : 3280, 3120 (N-H) ; 1675 (C=O ester) ; 1705 (C=O). ^{1}H-nmr (DMSO-D_6) : 10.55 (s, NH), 9.80 (s, NH), 7.85 (m, 2H,Ph), 7.60 (m, 3H,Ph), 6.66 (s, C=CH), 5.95 (s, C=CH), 3.76 (s, CO_2CH_3). ^{13}C-nmr (DMSO-D_6) : 177.7 ; 176.5 ; 174 ; 166.2 ; 150.5 ; 132.35; 128.98; 127.52 (C_6H_5) ; 114.83 (=CH) ; 91.88 (=CH) ; 52.14 (O-CH_3).

2-(2-Amino-2-p-chlorophenylethylidene)-5-carbomethoxymethylenethiazolin-4-one (compound Id)
Yield 40% ; m p 303°C ; ir (KBr) : 3270, 3100 (NH) ; 1682 (C=O ester); 1710 (C=O). ^{1}H-nmr (DMSO-D_6) : 10.52 (s, NH), 9.80 (s, NH), 7.70 (m, 4H,Ph), 6.67 (s, C=CH) , 5.92 (s, C=CH), 3.70 (s, CO_2CH_3). ^{13}C-nmr (DMSO-D_6) : 129.39, 129.00 (Cl C_6H_4) ; 114.70 (=CH) ; 91.20 (=CH) ; 52.10 (O-CH_3).

2-(2-Aminopropenylidene)-1,3-thiazin-4-one (compound IIa)
Yield 40% ; m p 248°C ; ir (KBr) : 3270, 3100 (N-H) ; 1645 (C=O) ; ^{1}H-nmr (DMSO-D_6) : 10,0 (s, 1H, NH) , 8.35 (s, 1H, NH) , 7.8 (d, 1H, CH =CH), 6.3 (d, 1H, CH=CH), 4.9 (s, 1H, =CH), 2.0 (s, 3H, CH_3).

^{13}C-nmr (DMSO-D_6) : 170.2 ; 167.7 ; 162.0 ; 137.9 (=CH) ; 118.1 (=CH) ; 91.85 (=CH) ; 21.68 (C-CH_3). Mass spectrum,m/e(70 ev, relative intensity) : 168 (7.5), 167 (74), 86 (9.2), 85 (18), 82 (42), 81 (100), 66 (18.8), 57 (22), 42 (34).

2-(2-Aminopropenylidene)-6-phenyl-1,3-thiazin-4-one (compound IIb)

Yield 30% ; mp 224°C ; ir (KBr) : 3240, 3040 (N-H) ; 1635 (C=O). ^{1}H-nmr (DMSO-D_6) : 10.0 (s, 1H, NH) ; 8.45 (s, 1H, NH) ; 7.50 (m, 5H, Ph) ; 6.65 (s, 1H, C=CH) ; 5.0 (s, 1H, =CH) ; 2.0 (s, 3H, CH_3). ^{13}C-nmr (DMSO-D_6) : 169.2 ; 167.8 ; 162.0 ; 135.1 ; 130.8; 129.3 ; 126 (p,m,o, Ph) ; 114.56 (=CH) ; 91.6 (=CH) ; 21.7 (C-CH_3).

2-(2-Aminopropen-2-ylidene)-3 H-4-methylthiazoline hydrobromide (compound III)

Yield 95% ; mp 155°C ; ir (KBr) : 3280, 3190, 3080 (N-H) ; 1655 (C=C) ; 1645 (C=C). ^{1}H-nmr (DMSO-D_6) 8.80, 8.50 (2s, 4H, NH); 5.40 (s, 1H, =CH); 4.0 (d, 1 Hz, 2H, =CH_2); 3.15 (t, 1 Hz, 1H, =CH); 2.35 (s, 3H, CH_3). Mass spectrum,m/e (70 ev, relative intensity) : (M-HBr : 154 (51)), 115 (28), 83 (68), (HBr : 80 (16)), 82 (16), 83 (68), 42 (100), 39 (32).

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