REACTIONS OF SOME 1-(4,5-DIHYDROIMIDAZOL-2-YL)AZOLES WITH AROYL AND ETHOXYCARBONYL ISOTHIOCYANATES [$]

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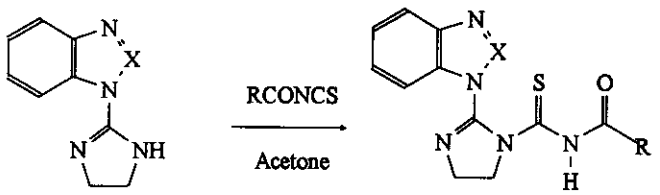
Abstract - Three components cyclocondensations of the imidazole derivative (**1c**) with aroyl isothiocyanates afforded 6,7,8,8a-tetrahydro-3-aroylimidazo[1,2-*a*][1,3,5]triazine-2,4(*3H,8H*)-dithiones (**5a-e**), while similar reaction with ethoxycarbonyl isothiocyanate led to the formation of ethyl 5-thioxo-2,3,8,9-tetrahydro-*5H*-diimidazo[1,2-*a*:1',2;-*c*]-[1,3,5]triazine-6-carboxylate (**10**).

As part of our continuing programme on the synthesis and biological screening of 2-imidazoline derivatives we have prepared a variety of condensed 4,5-dihydroimidazoles through different synthetic routs.[1-5] The aim of the present study was to synthesize some hitherto unexplored imidazo[1,2-*a*][1,3,5]triazine -2,4(*1H,3H*)-dithiones as potential inhibitors of dopamine β-hydroxylase. Previously Matsumura and co-workers reported the synthesis of 6,7,8,8a-tetrahydro-1,3-dialkylimidazo[1,2-*a*][1,3,5]triazine-2,4(*1H,3H*)-dithiones by the reactions of aliphatic isocyanates with anions generated from imidazoline-2-thione.[6] However, the corresponding aroyl derivatives have never been synthesized by this method. In practice, our attempt to use aroyl, instead of alkyl isothiocyanates, did not afford the desired products but only equivocal results under the similar conditions. Thus, we decided to investigate the reactions of 2-(4,5-dihydroimidazol-2-yl)azoles (**1a-c**)[7] with aroyl isothiocyanates involving an azole as a leaving group in cyclocondensation reactions. Preliminary experiments revealed that the reactivity of benzimidazole (**1a**) or benzotriazole derivative (**1b**) is too low for practical use as it produced relatively unstable adducts (**2a-d**) (Scheme 1).

However, the imidazole derivative **1c** has proved to be a good substrate for annelation of triazine ring to existing imidazoline base. The steps through which the starting compound (**1c**) was converted into the final products (**5a-e**) are represented in Scheme 2.

The experimental procedure is a simple addition of two-fold amount of isothiocyanate to a solution of **1c** in anhydrous pyridine. A mildly exothermic reaction takes place and the mixture is maintained at room temperature for 12 h. Crude product (**5**) is separated by suction and purified by single recrystallization from DMF. Compounds (**5a-e**) were obtained as orange crystals and their ir spectra showed carbonyl bands in the 1740 - 1745 cm^{-1} region. The structure of **5** was further confirmed by conversion to 2-oxoimidazoline (**7**) on treatment with refluxing aqueous dimethylformamide. That

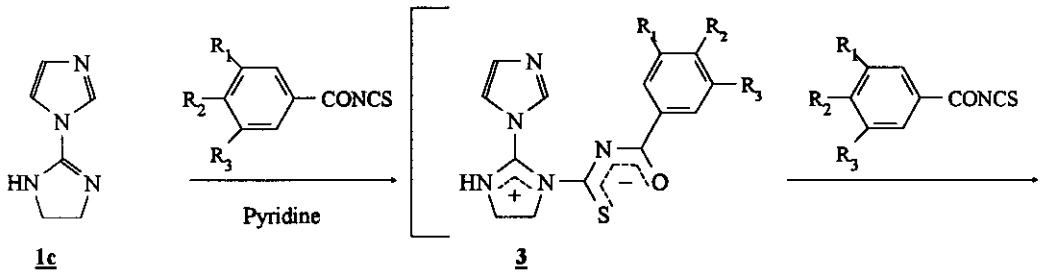
[$] *This paper is dedicated to Professor Alan R. Katritzky on the occasion of his 65th birthday.*



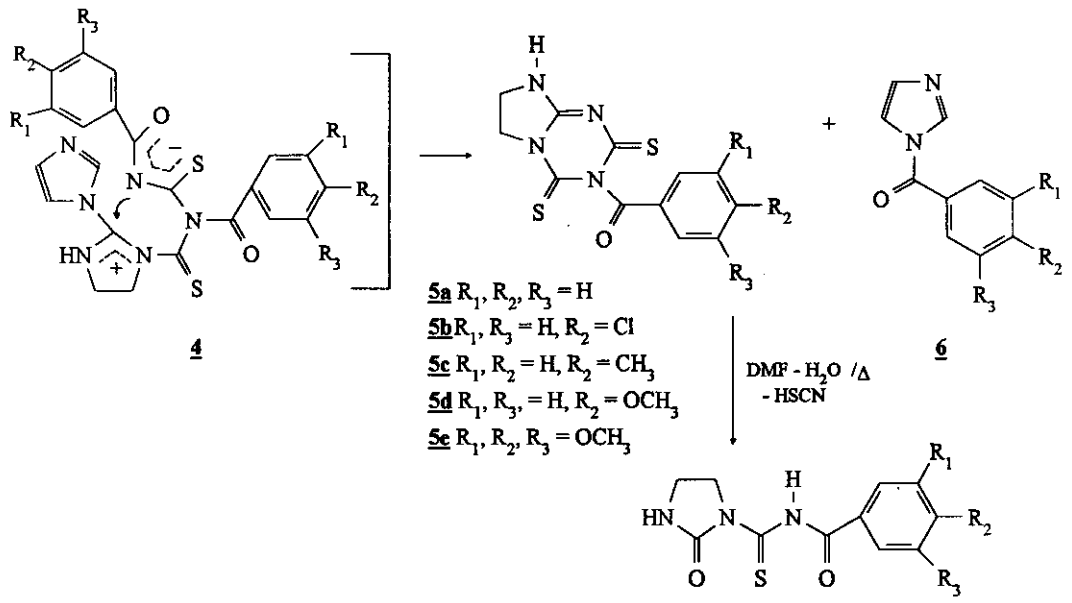
1a X = CH
1b X = N

2a X = CH, R = Ph
2b X = N, R = Ph
2c X = CH, R = OC_2H_5
2d X = N, R = OC_2H_5

Scheme 1



1c **3**



4

5a R_1, R_2, R_3 = H
5b R_1, R_3 = H, R_2 = Cl
5c R_1, R_2 = H, R_2 = CH_3
5d R_1, R_3, = H, R_2 = OCH_3
5e R_1, R_2, R_3 = OCH_3

6

DMF - H_2O /Δ
- HSCN

Scheme 2

7 R_1, R_2, R_3 = H

the product (7) was the same compound as that prepared on independent way by Wilhelm[8] was shown by its elemental analysis, spectral data and by the proximity of its melting point (208-210 °C) to that found by these earlier workers (210-211 °C). Attempted preparation of the corresponding 3-ethoxycarbonyl-imidazo[1,2-*a*]triazine-2,4-dithione by reacting 1c with ethoxycarbonyl isothiocyanate under similar conditions was not succesful. Trifunctional nature of alkoxycarbonyl

Table I. Physical ans Spectroscopic Data for 2a-d, 5a-e and 11.

Compd[a] No	mp (°C)	Yield (%)	^{1}H-nmr (DMSO-d_6/TMS) δ (ppm)
2a	177 - 180 (acetone-Et_2O)	57	3.5(m,2H,CH_2), 4.1(m,2H,CH_2), 7.4-8.4(m,9H, aromat.), 8.6(s,1H,CH).
2b[b]	166 - 169 (acetone)	70	3.5(m,2H,CH_2), 4.1(m,2H,CH_2), 7.6-8.0(m,7H, aromat.), 8.2-8.5(m,2H,aromat.).
2c	118 - 122 (acetone-Et_2O)	68	0.75(t, J=6.8 Hz, 3H,CH_3), 3.65(q, J=6.8 Hz, 2H,OCH_2), 3.95(t, J=7.5 Hz,2H, CH_2), 4.45(t, J=7.5 Hz, 2H,CH_2), 7.3-7.55(m,2H,aromat.), 7.6-7.9(m,2H,aromat.), 8.35(s,1H,CH).
2d	105 - 107 (acetone)	52	0.6(t,J=6.8 Hz,3H,CH_3), 3.4(q,J=6.8 Hz, 2H, OCH_2), 4.0(m,2H, CH_2), 4.5(m,2H,CH_2), 7.45-8.0(m,3H,aromat.), 8.15(m,1H,aromat.).
5a[c]	244 - 247 (DMF)	35	3.6(m,2H,CH_2), 4.3(m,2H,CH_2), 7.6(m,3H, aromat.), 8.5(m,2H,aromat.).
5b	239 - 242 (DMF)	31	3.6(m,2H,CH_2), 4.2(m,2H,CH_2), 7.7(d,J=8.4 Hz, 2H, aromat.), 8.4(d,J=8.4 Hz, 2H,aromat.).
5c	232 - 234 (DMF)	40	2.4(s,3H,CH_3), 3.55(m,2H,CH_2), 4.2(m,2H, CH_2), 7.5(d,J=8.2 Hz, 2H,aromat.), 8.35 (d,J=8.2 Hz, 2H,aromat.).
5d	218 - 221 (DMF)	17	3.6(m,2H,CH_2), 3.9(s,3H,OCH_3), 4.3(m,2H, CH_2), 7.1(d,J=8.5 Hz 2H,aromat.), 8.45 (d, J=8.5 Hz, 2H,aromat.).
5e	238 - 241 (DMF)	27	3.6(m,2H,CH_2), 3.85(s,3H,OCH_3), 3.95(s,6H, OCH_3), 4.2(m,2H,CH_2), 7.8(s,2H,aromat.).
11[d]	173 - 176 (benzene)	29	1.25(t,J=7.0 Hz, 3H,CH_3), 4.25(q,J=7.0 Hz, 2H,OCH_2), 3.5-4.5(m, 8H,CH_2).

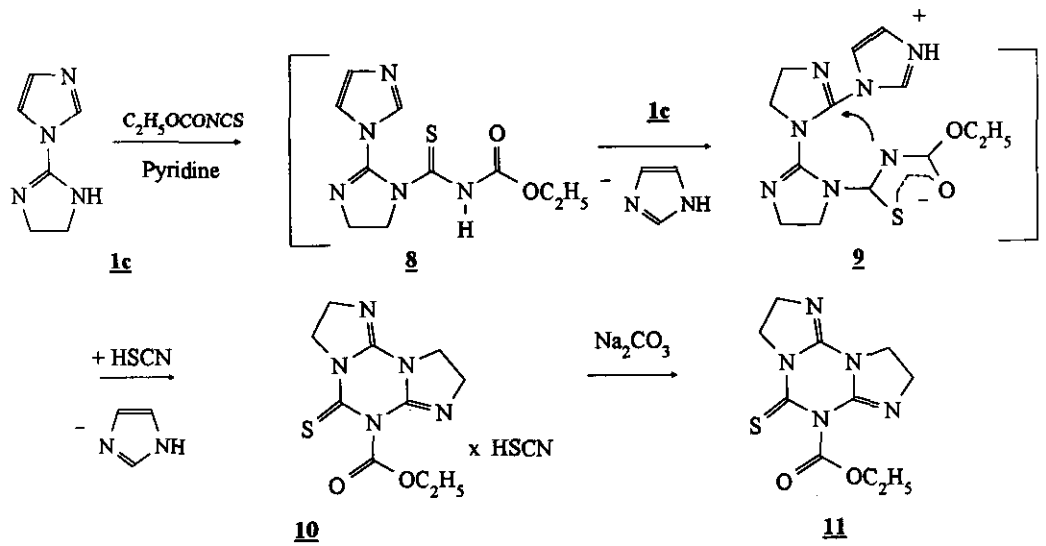
[a] Satisfactory microanalysis obtained for all compounds prepared.

[b] ms, (EI) m/z: 350(M^+,0.2), 322(11), 231(86), 211(10(, 195(16), 194(15), 119(100), 105(21), 91(58).

[c] ms, (EI) m/z: 290(M^+,38), 247(45), 214(10), 162(9), 105(11), 104(17), 86(10), 85(100), 67(36).

[d] ms, (EI) m/z: 267(M^+,100), 223(57), 195(39.5), 194(65), 190(16), 110(10), 44(18);

^{13}C-nmr ($CDCl_3$) δ = 14.06(CH_3), 37.4(CH_2), 43.8(CH_2), 48.9(CH_2), 49.7(CH_2), 62.7(OCH_2), 144.7(C-sp_2), 149.3 (C-sp_2), 150.3(C-sp_2), 182.2(C=S).



Scheme 3

isothiocyanates enables them to participate in a variety of reactions with loss of the elements of thiocyanic acid.[9] Thus, the reaction led to a plethora of products with no major component having the tlc mobility expected for the desired imidazo[1,2-*a*]triazinedithione. However, after washing of the reaction mixture with ethyl ether and subsequent treatment of the oily residue with acetone, a new compound was separated to which we assigned structure (**10**) on the basis of analytical and spectral data. The formation of ethyl 5-thioxo-2,3,8,9-tetrahydro-5*H*-diimidazo[1,2-*a*:1',2'-*c*][1,3,5]triazine-6-carboxylate (**10**) may be explained by the mechanistic considerations depicted in Scheme 3. The initially formed adduct **8** is assumed to react with a second molecule of **1c** to give intermediate (**9**) which undergoes cyclization in which external protonation of the imidazole aids leaving-group expulsion. Salt (**10**) thus obtained was converted into the free base (**11**) by treatment with 10% sodium carbonate solution.

Physical and spectroscopic data of the compounds (**2a-d**, **5a-e** and **11**) are presented in table 1.

ACKNOWLEDGMENTS

We thank KBN, Grant No 4 0833 91 01, for financial support.

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Received, 24th September, 1993