ON THE REACTION OF 2-CHLORONICOTINIC ACID WITH 2-AMINOBENZOTHIAZOLE

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Abstract - The results of the reaction of 2-chloronicotinic acid with a series of 2-aminobenzothiazoles are reported. Under reflux of xylene the major product is the corresponding N-(2-benzothiazolyl)-1,2-dihydro-2-oxonicotinamide. Its structure is confirmed by an alternative synthesis and a possible explanation for its formation is provided. The results of the reaction of 2-aminobenzothiazole with 2-chloronicotinoyl chloride and methyl 2-chloronicotinate are also summarized.

2-Chloronicotinic acid is an ambident electrophilic reagent, the reactions of which with aliphatic and aromatic amines are well documented and known to yield 2-aminonicotinic acids,[1] along with minor amounts of the corresponding 2-aminonicotinamides[2].

It is also known that when 2-chloronicotinoyl chloride is made to react with amines, 2-chloronicotinamides are obtained[3]. Thus, the following decreasing order of electrophilicity towards amines can be established: $-COCl > C_2 - Cl > COOH$

In both cases, when ambident nucleophilic reagents are used, fused policyclic compounds may result 1,4,5.

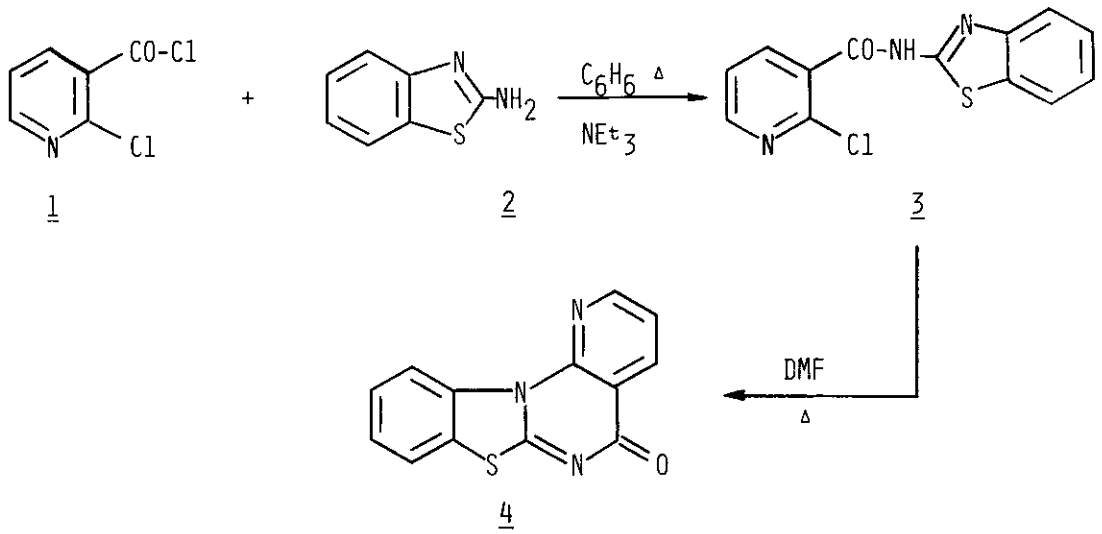
One of these dinucleophiles is 2-aminobenzothiazole, and according to this framework, the reaction of 2-chloronicotinoyl chloride 1 with 2-aminobenzothiazole 2 leads to the expected N-(2-benzothiazolyl)-2-chloronicotinamide[6] 3 which can be cyclized to the corresponding 5-oxo-5H-pyrido[3',2':5,6] pyrimido [2,1-b] benzothiazole 4 upon heating in DMF[6]. (Scheme 1).

Nevertheless, the reaction of 2-chloronicotinic acid with 2-aminobenzothiazole proved to be less straightforward since neither of the expected products (7a or 7b) could be identified.

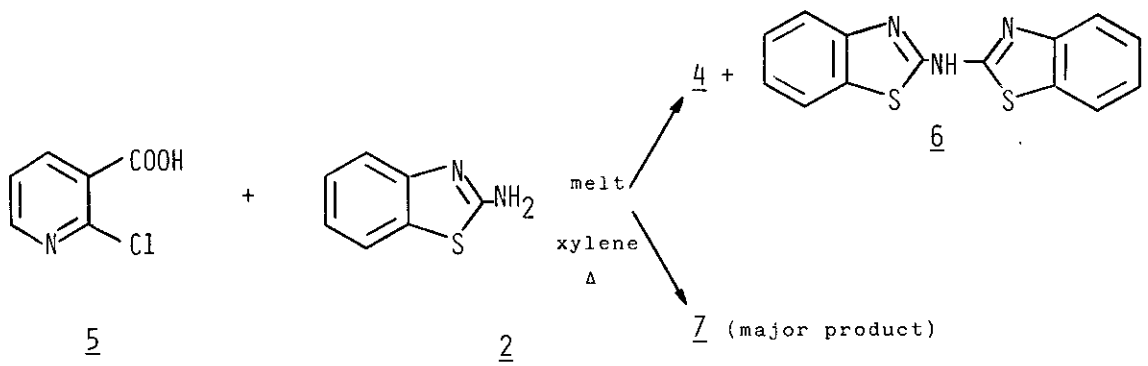
This was in contrast with the previous report[4] in which the reaction of 2-chloronicotinic acid with 2-amino-4-arylthiazoles gave 3-aryl-5-oxo-5H-pyrido[2,3-d]thiazolo[3,2-a]pyrimidines, though the stated yields were low (12-18%) and no characterization of byproducts was reported.

Our experience was that when the reaction of 2-chloronicotinic acid 5 with 2 was performed by melting the mixture, without any solvent, two main products resulted (Scheme 2), one of them being the angular fused derivative 4. Evolution of ammonia was observed and led us to suspect that 2,2'-iminobis (benzothiazole)6 might have been formed, since this type of reaction is not without precedent in the literature[7]. Its physical and spectral properties were identical to those previously described[8]. The reaction was carried out under a variety of conditions but complex mixtures resulted in every case, and only under reflux of xylene was a major product of unknown structure (labelled 7) obtained, along with minor amounts of compounds 3, 4 and 6 (Scheme 2).

According to the pattern of reactivity previously stated, two structures could be devised for the resulting major product, namely, that of 2-(2-benzothiazolylamino)nicotinic acid 7a, or that of 5-oxo-5H-pyrido[2',3':4,5]pyrimido[2,1-b]benzothiazole 7b. Elemental analysis and molecular ion determination ruled out the linear fused structure 7b and supported that of 7a. Nevertheless, neither the ^{1}H-nmr spectrum, nor the mass spectral fragmentations seemed to point to structure 7a, as no fragment ions at M-18, M-44 or M-45 were observed; instead, successive losses of 28 mass units from molecular and fragment ions. Furthermore, in the ^{1}H-nmr spectrum of 7 the δ and J values for pyridi-



- Scheme 1 -

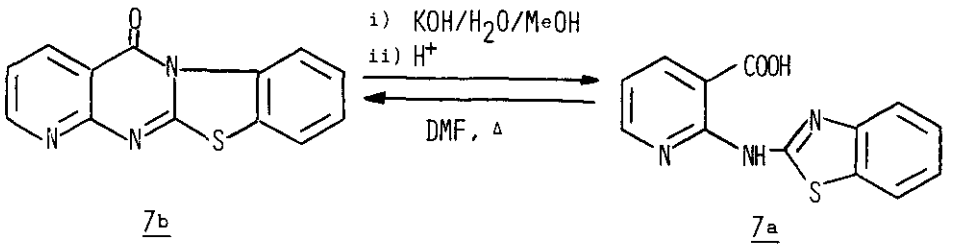


- Scheme 2 -

ne ß-proton strongly suggested the presence of a 2-pyridone ring.

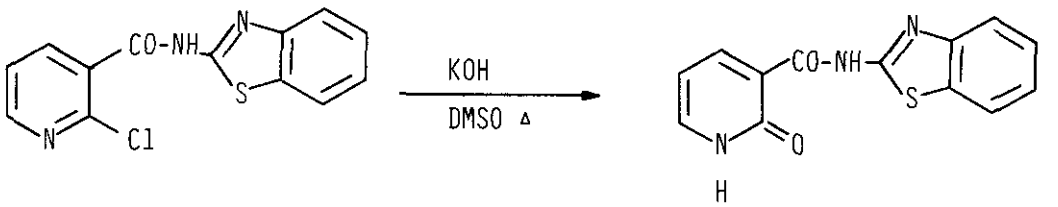
That compound 7 was not structure 7a was confirmed by its inability to undergo cyclodehydration on treatment with polyphosphoric acid, dicyclohexylcarbodiimide or thionyl chloride[5] and by an independent synthesis of 7a from 7b[9] shown in scheme 3. As additional proof, 7a was converted quantitatively into 7b on heating in DMF.

Finally, and in accordance with the aforementioned data, compound 7 was assigned a structure of N-(2-benzothiazolyl)-1,2-dihydro-2-oxonicotinamide, which was confirmed by an independent synthesis from compound 3, involving hydroxylation with potassium hydroxide in DMSO[10] (Scheme 4).



7b 7a

- Scheme 3 -



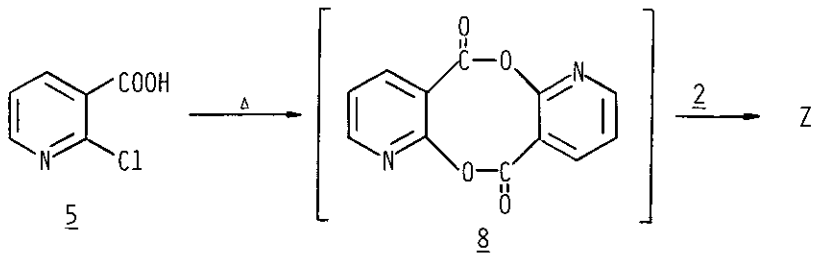
3 7

- Scheme 4 -

One way of accounting for the formation of 7 from 2-chloronicotinic acid and 2-aminobenzothiazole implies the existence of 8 as a reactive intermediate, resulting from the thermic degradation of 5 (Scheme 5).

A similar explanation has been put forward in the case of the reaction of 2-chloronicotinic acid with sterically-hindered anilines[2]. However, steric hindrance cannot be invoked here, but it can be supposed that all the factors working against the attack of the amino group -such as the weak nucleophilicity of 2-aminobenzothiazole- favour the degradation of 5 to yield 8.

It can therefore be stated that 2-aminobenzothiazole is not nucleophilic enough to substitute the chlorine atom in 2-chloronicotinic acid; additional support for this affirmation is provided by the fact that there is no reaction between 2-aminobenzothiazole and methyl 2-chloronicotinate, a substrate which shows a similar reactivity at C-2 but which cannot undergo self-condensation to 8. In fact starting materials were recovered nearly unchanged after 40 h at reflux of xylene.



5 8

- Scheme 5 -

Similar results were observed with a series of substituted 2-aminobenzothiazoles.

EXPERIMENTAL

Melting points were determined using a Büchi 510 apparatus and are uncorrected. I.R. spectra were recorded on a Perkin-Elmer 283 instrument. ^{1}H-N.M.R. spectra were obtained on a Perkin-Elmer R-12-B spectrometer with TMS as internal reference. Mass spectra were recorded using a Hewlett-Packard 5930 -A spectrometer.

Preparation of N-(2-Benzothiazolyl)-1,2-dihydro-2-oxonicotinamides

General Method A: 0.01 mol (1.57 g) of 2-chloronicotinic acid 5 and 0.01 mol of the corresponding 2-aminobenzothiazole were dissolved in 50 ml of xylene and heated under reflux for 40 h. The mixture was the cooled and the precipitate filtered off, washed with benzene and ethanol and recrystallized from DMF.

General Method B: 2mmol of the corresponding N-(2-benzothiazolyl)-2-chloronicotinamide[6] and 16 mmol (0.896 g) of potassium hydroxide were dissolved in 10 ml of DMSO and heated at 150°C for 3 h. The mixture was then cooled, poured into water (20 ml) and acidified with hydrochloric acid until pH 5. The precipitate thus obtained was filtered off, dried and recrystallized from DMF.

N-(2-Benzothiazolyl)-1,2-dihydro-2-oxonicotinamide: mp > 300°C; yield 21% (method A), 57% (method B); ir (nujol) 1680, 1635 cm^{-1}; ^{1}H-nmr(DMSO-d_6)δ 13.7 (s, 1 H), 8.55 (dd, J = 7 Hz, J'= 2 Hz, 1 H), 8.1-7.1 (m, 5 H), 6.65 (dd, J = 7 Hz, J' = 6,5 Hz, 1 H) ; ms, m/z 271(M^+, 89%), 243(21), 150(100), 122(100), 94(30), 66(15); calc. for $C_{13}H_9N_3O_2S$: C,57.55% ; H,3.34 ; N,15.49 ; found: C,57.38 ; H,3.56 ; N,15.39

N-(6-Methoxy-2-benzothiazolyl)-1,2-dihydro-2-oxonicotinamide: mp > 300°C; yield 28% (A); 54% (B); ir (nujol) 1685, 1630 cm^{-1}; ^{1}H-nmr(TFA)δ 8.85 (dd, J = 7 Hz, J'= 2 Hz, 1 H); 8.0 (dd, J = 6, 5 Hz, J'= 2 Hz, 1 H), 7.8-7.2(m, 3 H), 7.0(dd, J = 7 Hz, J'= 6,5 Hz, 1 H), 4.0(s, 3 H).

N-(6-Methyl-2-benzothiazolyl)-1,2-dihydro-2-oxonicotinamide: mp > 300°C; yield 32%(A); ir (nujol) 1680, 1630 cm^{-1}; ^{1}H-nmr(TFA)δ 9.0(dd, J = 7 Hz, J'= 2 Hz, 1 H), 8.15 (dd, J = 6,5 Hz, J'= 2 Hz,1 H), 8.0-7.6 (m, 3 H), 7.1(dd, J = 7 Hz, J'= 6,5 Hz, 1 H), 2.6 (s, 3 H); ms, m/z 285(M^+, 100%), 257(10), 164(100), 122(100), 94(49), 66(26); calc. for $C_{14}H_{11}N_3O_2S$: C, 58.93% ; H, 3.88 ; N, 14.73 ; found: C, 59.06 ; H, 3.75 ; N, 14.58.

N-(4-Chloro-2-benzothiazolyl)-1,2-dihydro-2-oxonicotinamide: mp > 300°C; yield 49 %(B); ir (nujol) 1680, 1630 cm^{-1}; ^{1}H-nmr(TFA)δ 8.85(dd, J = 7 Hz, J'= 2 Hz, 1 H), 8.1-7.5 (m, 4 H), 6.95 (dd, J = 7 Hz, J'= 6,5 Hz, 1 H).

N-(5,6-Dimethyl-2-benzothiazolyl)-1,2-dihydro-2-oxonicotinamide: mp > 300°C; yield 50%(B); ir (nujol) 1680, 1630 cm^{-1}; ^{1}H-nmr(TFA) δ 8.95(dd, J = 7 Hz, J'= 2 Hz, 1 H), 8.1 (dd, J = 6,5 Hz, J'= 2 Hz, 1H),

7.8(s, 1 H), 7.65(s, 1 H), 7.1(dd, J = 7 Hz, J'= 6,5 Hz, 1 H), 2.5(s, 6 H).

Preparation of 2-(2-Benzothiazolylamino)nicotinic Acids (General Method)

1 mmol of the corresponding 5-oxo-5H-pyrido[2',3': 4,5]pyrimido[2,1-b]benzothiazole[9] was added to a solution of potassium hydroxide (0.146 g) in 5 ml of 1/1: methanol/water. The suspension was refluxed for 2.5 h, then cooled and the solution obtained was acidified with 6N hydrochloric acid until pH 4. The white precipitate was recovered by filtration, washed with water, dried and recrystallized from n-butanol.

2-(2-Benzothiazolylamino)nicotinic Acid: mp 261-263°C; yield 98%; ir nujol 1700, 1610 cm^{-1}; ^{1}H-nmr (DMSO - d_6) δ 8.55(dd, J = 5 Hz, J'= 2 Hz, 1 H), 8.35 (dd, J = 7.5 Hz, J'= 2 Hz, 1 H), 8.0 - 6.5 (m, 6 H); calc. for $C_{13}H_9N_3O_2S$: C, 57.55% ; H, 3.34 ; N, 15.49 ; found: C, 57.70 ; H, 3.41 ; N, 15.30.
2-(6-Methyl-2-benzothiazolylamino)nicotinic Acid: mp 278-280°C; yield 96%; ir (nujol) 1700,1620 cm^{-1} ; ^{1}H-nmr (DMSO - d_6) δ 8.6(dd, J = 5 Hz, J'= 2 Hz, 1 H), 8.4 (dd, J = 7,5 Hz, J'= 2 Hz, 1 H), 7.8 - 7.0 (m, 4 H), 2.4 (s, 3 H) ; ms, m/z 285(M^+, 97%), 267(100), 241(68), 240(59), 239(19), 133.5 ($M-18^{7++}$, 32) ; calc. for $C_{14}H_{11}N_3O_2S$: C, 58.93% ; H, 3.88 ; N, 14.73; found C, 58.78 ; H, 3.70 ; N, 14.91.

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Received, 26th July, 1985