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Synthesis of 2-Acylaminobenzimidazoles from Acyl Isothiocyanates and *o*-Phenylenediamine

P. KUTSCHY, V. FICERI, and M. DZURILLA

Department of Organic Chemistry, Faculty of Natural Sciences, P. J. Šafárik University, SK-041 67 Košice

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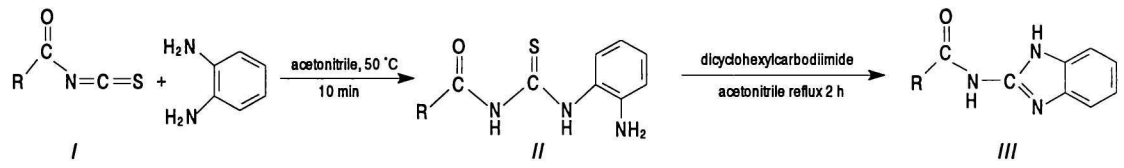
Acyl isothiocyanates react with *o*-phenylenediamine in anhydrous acetonitrile in the presence of dicyclohexylcarbodiimide as cyclodesulfurizing agent with the formation of acyl derivatives of 2-aminobenzimidazole. Intermediates of the reaction are corresponding *N*-(2-aminophenyl)-*N'*-acylthioureas readily formed at laboratory temperature, which cyclize to benzimidazole derivatives by the action of dicyclohexylcarbodiimide in boiling acetonitrile.

Amongst 2-aminobenzimidazole derivatives there are some compounds exhibiting an expressive biological activity. For instance, methyl *N*-(2-benzimidazolyl)carbamate is used as broad spectrum systemic fungicide [1] and some of its derivatives are known as anthelmintics [2]. These compounds can be prepared by the reaction of *o*-phenylenediamine derivatives with methyl *N*-cyanocarbamate [3]. In the year 1977 appeared a paper reporting on the preparation of 2-alkylamino- and 2-arylaminobenzimidazoles from *N*-(2-aminophenyl)-*N'*-substituted thioureas by the action of dicyclohexylcarbodiimide as cyclodesulfurizing agent in boiling benzene [4]. This approach was later applied in the synthesis of pyrimidine analogues of benzimidazoles from 4,5-diaminopyrimidine derivatives and methoxycarbonyl isothiocyanate under reflux in acetonitrile in the presence of dicyclohexylcarbodiimide [5]. Starting from this knowledge and in continuation of our previous research on acyl isothiocyanates we have studied the possibility of employment of different acyl isothiocyanates in the synthesis of 2-acylaminobenzimidazoles *via* the reaction with *o*-phenylenediamine and subsequent cyclodesulfurization by dicyclohexylcarbodiimide. We found that acyl isothiocyanates *I* readily react with *o*-phenylenediamine in dry acetonitrile at laboratory temperature with the formation of *N*-(2-aminophenyl)-*N'*-acylthioureas (*II*). Thioureas *IId* and *IIf* were also prepared independently by the reaction of *o*-phenylenediamine with isothiocyanates *Id* and *If* in benzene. Addition of dicyclohexylcarbodiimide to a solution of independently prepared thiourea or to a solution of not isolated thiourea in acetonitrile at 50 °C and following reflux of the reaction mixture for 2 h afforded 2-acylaminobenzimidazoles *III* (Scheme 1). The above-mentioned work [5] does not describe a detailed procedure. According to our experience for



I *II* *III*

R = CH_3 (*a*), $CH_3CH{=}CH$ (*b*), C_6H_5 (*c*), 4-Cl-C_6H_4 (*d*), 2,6-di-F-C_6H_3 (*e*), $C_6H_5CH{=}CH$ (*f*), 4-$CH_3C_6H_4CH{=}CH$ (*g*), 2-Cl-$C_6H_4CH{=}CH$ (*h*), 4-Cl-C_6H_4 (*i*), 2-naphthyl (*j*), 2-thienyl (*k*), 3-chloro-2-thienyl (*l*), 5-chloro-2-thienyl (*m*), 3-chloro-2-benzo[*b*]thienyl (*n*).

Scheme 1

achieving of high yield of product it is important to add *o*-phenylenediamine to an acetonitrile solution of isothiocyanate and only after warming, when all isothiocyanate has reacted, to add dicyclohexylcarbodiimide. This finding corresponds to the report dealing with cycloaddition of dicyclohexylcarbodiimide to acyl isothiocyanates [6]. If dicyclohexylcarbodiimide is added while an unreacted acyl isothiocyanate is present, it could lead to the formation of other products. We have found that the reaction can be advantageously performed as a one-pot synthesis (procedure *A*), starting from corresponding acyl chloride which is transformed in dry acetonitrile by the action of KSCN to acyl isothiocyanate. Obtained solution is then treated with *o*-phenylenediamine and dicyclohexylcarbodiimide. 2-Acylaminobenzimidazoles *III* are obtained in the yields 35—94 % (Table 1). The use of isolated acyl isothiocyanates (procedure *B*) is less advantageous, because the yields (related to acyl chlo-

Table 1. 2-Acylaminobenzimidazoles *III*

Compound	R	Formula M_r	w_i(calc.)/% w_i(found)/%			Procedure *A* %	M.p./°C Solvent[a]	IR, $\tilde{\nu}$/cm^{-1} C=O
			C	H	N			
IIIa[b]	CH_3	$C_9H_9N_3O$ 175.2	61.70 61.51	5.18 5.17	23.99 23.84	54	296—298 A	1680
IIIb	$CH_3CH{=}CH$	$C_{11}H_{11}N_3O$ 201.2	65.66 65.53	5.51 5.75	20.88 20.69	59	250—252 E	1680
IIIc	C_6H_5	$C_{14}H_{11}N_3O$ 237.3	70.87 70.98	4.67 4.56	17.71 17.64	45	242—244 M	1670
IIId[b,c]	4-Cl-C_6H_4	$C_{14}H_{10}ClN_3O$ 271.7	61.89 61.70	3.71 3.63	15.47 15.35	60	250—251 M	1660
IIIe[d]	2,6-di-F-C_6H_3	$C_{14}H_9F_2N_3O$ 273.2	61.54 61.62	3.32 3.28	15.38 15.45	68	280—282 A	1670
IIIf[d]	$C_6H_5CH{=}CH$	$C_{16}H_{13}N_3O$ 263.3	72.99 73.15	4.98 4.91	15.96 16.08	77	246—248 E	1655
IIIg	4-CH_3-$C_6H_4CH{=}CH$	$C_{17}H_{15}N_3O$ 277.3	73.63 73.49	5.45 5.57	15.15 15.02	42	265—267 M	1670
IIIh	2-Cl-$C_6H_4CH{=}CH$	$C_{16}H_{12}ClN_3O$ 297.7	64.54 64.59	4.06 3.90	14.11 14.32	58	267—268 A	1670
IIIi	4-Cl-$C_6H_4CH{=}CH$	$C_{16}H_{12}ClN_3O$ 297.7	64.54 64.64	4.06 3.96	14.11 13.98	35	279—281 A	1670
IIIj	2-Naphthyl	$C_{18}H_{13}N_3O$ 287.3	75.25 75.41	4.56 4.38	14.63 14.80	71	280—282 A	1650
IIIk	2-Thienyl	$C_{12}H_9N_3OS$ 243.3	59.24 59.31	3.73 3.88	17.27 17.13	94	309—311 A	1705
IIIℓ[d]	3-Chloro-2-thienyl	$C_{12}H_8ClN_3OS$ 277.7	51.90 51.72	2.90 2.82	15.13 15.27	45	227—229 M	1640
IIIm[d]	5-Chloro-2-thienyl	$C_{12}H_8ClN_3OS$ 277.7	51.90 51.75	2.90 3.08	15.13 15.26	60	252—253 E	1670
IIIn[d]	3-Chloro-2-benzo[*b*]thienyl	$C_{16}H_{10}ClN_3OS$ 327.8	58.63 58.49	3.08 3.21	12.82 12.62	78	282—283 A	1620

a) A — acetone, E — ethanol, M — methanol. *b*) ^{1}H NMR: δ(*IIIa*): 2.42 (s, 3H, CH_3), 7.44 and 7.80 (m, 4H, C_6H_4), 12.09 (s, 2H, NH); δ(*IIId*): 7.50—7.80 and 8.55 (m, 8H, 2 × C_6H_4); δ(*IIIℓ*): 7.42 and 7.93 (d, 2H, J_{AB} = 5 Hz, CH=CH), 7.63 (m, 4H, C_6H_4); δ(*IIIm*): 7.62 (m, 6H, =CH—CH— and C_6H_4), 12.67 (s, 1H, NH). *c*) ^{13}C NMR: δ(*IIId*): 112.67, 121.30, 128.16, 130.09, 132.75, 134.24, and 136.41 (2 × C_6H_4), 150.03 (C=N), 168.73 (C=O). *d*) Mass spectrum, *m/z* (I_r/%) *IIIe*: 273 (36) $M^{+\bullet}$, 254 (13) $[M - F]^+$, 141 (100) [2,6-di-F-$C_6H_3CO]^+$, 113 (20) [2,6-di-F-$C_6H_3]^+$. *IIIf*: 263 (86) $M^{+\bullet}$, 131 (100) $[C_6H_5CH{=}CHCO]^+$, 103 (52) $[C_6H_5CH{=}CH]^+$. *IIIm*: 277 (47) $M^{+\bullet}$, 145 (100) [5-chloro-2-thienocarbonyl]$^+$. *IIIn*: 328 (24) $M^{+\bullet}$, 292 (100) $[M - Cl]^+$, 195 (58) [3-chloro-2-benzo[*b*]thienocarbonyl]$^+$.

ride) are lower by about 10—15 % compared to procedure *A*.

Structure of the prepared 2-acylaminobenzimidazoles *III* was confirmed by elemental analysis, mass spectrometry, IR, ^{1}H NMR, and ^{13}C NMR spectroscopy (Table 1). In mass spectra of compounds *IIIe*, *IIIf*, *IIIm*, and *IIIn* there are present the peaks of molecular ions with *m/z* values corresponding to expected molecular masses and fragment peaks of acyl groups. The IR spectra exhibit absorption bands of carbonyl group at $\tilde{\nu}$ = 1620—1705 cm^{-1}. Due to insolubility of most of prepared benzimidazole derivatives, the ^{1}H and ^{13}C NMR spectra were recorded only at limited number of compounds (Table 1). Obtained NMR data for compounds *IIIa*, *IIId*, *III*ℓ, and *IIIm* are in agreement with the structure of 2-acylaminobenzimidazoles. Structure of compounds *III* was also confirmed by alkaline hydrolysis of derivative *IIIf* which afforded 2-aminobenzimidazole having the melting point, IR and ^{1}H NMR spectra identical with an authentic sample [7, 8].

EXPERIMENTAL

Starting isothiocyanates were prepared according to the literature: *Ia* [9], *Ib* [10], *Ic* [11], *Id* [12], *Ie* [13], *If* [14], *Ig* [15], *Ih* [16], *Ii* [16], *Ij* [17], *Ik* [18], *Im* [16], *In* [19]. Infrared absorption spectra were recorded on an IR 75 spectrometer (Zeiss, Jena) in KBr pellets. ^{1}H NMR (*IIIa*, *IIId*, *III*ℓ, *IIIm*) and ^{13}C NMR (*IIId*) spectra were taken in hexadeuterodimethyl sulfoxide using tetramethylsilane as internal standard on Tesla BS 487A (80 MHz) and Tesla BS 567 (25 MHz) spectrometers, respectively. Mass spectra were recorded on a JMS-100D spectrometer (Jeol) at ionization energy 70 eV. The reaction course was monitored by thin-layer chromatography on Silufol plates (Kavalier).

3-Chloro-2-thienocarbonyl Isothiocyanate (*I*ℓ)

3-Chloro-2-thienocarbonyl chloride (1.54 g; 8.5 mmol) in anhydrous acetone (10 cm^3) was added at room temperature to a solution of potassium thiocyanate (0.83 g; 8.5 mmol) in anhydrous acetone (30 cm^3). After stirring for 5 min, benzene (40 cm^3) was added until turbidity disappeared and the precipitate of potassium chloride was filtered off. The solvent was evaporated and the residue was crystallized from hexane. Yield 1.1 g (64 %), m.p. = 43—45 °C. For $C_6H_2ClNOS_2$ (M_r = 203.7) w_i(calc.): 35.38 % C, 0.99 % H, 6.90 % N; w_i(found): 35.51 % C, 1.12 % H, 6.74 % N. IR spectrum ($CHCl_3$), $\tilde{\nu}$/cm^{-1}: 1953 ν(N=C=S), 1679 ν(C=O). ^{1}H NMR spectrum ($CDCl_3$), δ: 7.75 and 7.77 (d, 1H and d, 1H, J_{AB} = 5 Hz, —CH=CH—).

N-(2-Aminophenyl)-*N*′-acylthioureas *IId*, *IIf*

Isothiocyanate *Id* or *If* (10.57 mmol) in benzene (25 cm^3) was added dropwise within 10 min under stirring to a solution of *o*-phenylenediamine (1.14 g; 10.57 mmol) in benzene (50 cm^3). After 25 min the separated precipitate was filtered off, washed with benzene and crystallized from an appropriate solvent.

N-(2-Aminophenyl)-N′-(4-chlorophenyl)thiourea (IId), yield 83 %, m.p. = 191—193 °C (benzene). For $C_{14}H_{12}ClN_3OS$ (M_r = 305.8) w_i(calc.): 54.99 % C, 3.96 % H, 13.74 % N; w_i(found): 55.12 % C, 3.79 % H, 13.87 % N. IR spectrum (KBr), $\tilde{\nu}$/cm^{-1}: 1485 ν(NHCS), 1670 ν(C=O).

N-(2-Aminophenyl)-N′-(3-phenylpropenoyl)thiourea (IIf), yield 69 %, m.p. = 204—206 °C (methanol). For $C_{16}H_{15}N_3OS$ (M_r = 297.4) w_i(calc.): 64.62 % C, 5.08 % H, 14.13 % N; w_i(found): 64.83 % C, 5.32 % H, 13.91 % N. IR spectrum (KBr), $\tilde{\nu}$/cm^{-1}: 1530 ν(NHCS), 1670 ν(C=O).

2-Acylaminobenzimidazoles *IIIa—IIIn*

Procedure A: Corresponding acyl chloride (4.78 mmol) was added at room temperature to a solution of potassium thiocyanate (0.47 g; 4.78 mmol) in anhydrous acetonitrile (7 cm^3). After stirring for 10 min *o*-phenylenediamine (0.52 g; 4.78 mmol) was added and the reaction mixture was heated up to 50 °C. Dicyclohexylcarbodiimide (0.97 g; 4.78 mmol) was added and the mixture was refluxed for 2 h. Separated solid was filtered off, washed with 15 cm^3 of a hot solution of methanol—water (φ_r = 1 : 1). Product was dried and crystallized from an appropriate solvent (Table 1).

Procedure B: *o*-Phenylenediamine (0.52 g; 4.78 mmol) was added to a solution of corresponding acyl isothiocyanate (4.78 mmol) in anhydrous acetonitrile (7 cm^3) at room temperature and then the preparation of the product was continued according to procedure *A*. Yield 20—75 %.

Procedure C: Dicyclohexylcarbodiimide (0.35 g; 1.68 mmol) was added under stirring at 50 °C to a solution of thiourea *IId* or *IIf* (1.68 mmol) in anhydrous acetonitrile (10 cm^3) and the mixture was refluxed for 2 h. The product was isolated as described in procedure *A*. Yield 55 % (*IIId*) and 75 % (*IIIf*).

Hydrolysis of 2-(3-Phenylpropenoylamino)-benzimidazole *IIIf*

Benzimidazole derivative *IIIf* (150 mg; 0.57 mmol) was dissolved in the solution of sodium hydroxide (50 mg; 1.25 mmol) in ethanol (10 cm^3) and the mix-

ture was stirred at room temperature for 10 min. The reaction mixture was poured into cold water (50 cm^3). Precipitated 2-aminobenzimidazole was filtered off, dried and crystallized from the ethanol—water mixture. Yield 75 mg (93 %), m.p. = 233—235 °C. The properties of obtained product are identical with an authentic sample [7, 8].

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Synthesis and the ^{13}C NMR Spectra of *N,N′*-Disubstituted Benzoylthioureas and Their Seleno and Oxo Analogues

J. IMRICH, T. BUŠOVÁ, P. KRISTIAN, and J. DŽARA

Department of Organic Chemistry, Faculty of Natural Sciences, P. J. Šafárik University, SK-041 67 Košice

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The influence of substituents on the ^{13}C NMR chemical shift values of the aromatic ring carbons and —CO—NH—C(=X)— groups (X = S, Se, O) of a series of 27 *N*-benzoyl-*N′*-(Y-aryl)- and -*N′*-alkylthioureas, selenoureas, ureas, thiourethanes and isothioureas was investigated. As found, the substituents in *N*-benzoyl-*N′*-(4-Y-phenyl)thio(seleno)ureas do not considerably influence the ^{13}C NMR chemical shifts of C=X and C=O carbons; the marked substituent effect is observed for the aromatic ring carbons only. This conclusion was also confirmed by correlations with χ_s and σ_p^+ constants of substituents. Differences between the benzoyl δ(CO) values of *N′*-monosubstituted and *N′,N′*-disubstituted thioureas indicate the existence of an intramolecular hydrogen bond in the acylthiourea grouping, namely between the benzoyl CO and the N′H groups. The ^{13}C NMR chemical shift values of C=Se carbons in *N*-benzoyl-*N′*-(4-Y-phenyl)selenoureas are higher than those of the analogous C=S carbons of the corresponding thioureas. The ^{13}C spectral chemical shift increments $\Delta\delta$ of —NHCSNHCOPh and —NHCSeNHCOPh groupings on the benzene ring were calculated.

Acylthioureas are known precursors of nitrogen or sulfur-containing heterocycles because of their reactive —CONHCSNH— grouping. Cyclization of acylthioureas can be well observed by ^{13}C NMR spectroscopy. This paper presents the study concerning the influence of substituents of the —CONHC(=X)NH— grouping (X = S, Se, O) on the chemical shift values of C=X and C=O groups and aromatic ring carbons in the *N*-benzoyl-*N′*-substituted thioureas *I, II,* selenoureas *III*, and isothioureas *V*.