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Cu-CATALYZED REACTIONS OF 2-IMIDAZOLETHIONES, 2-AMINBENZOTHIAZOLES AND 2-AMINO-1-BENZYLBENZOIMIDAZOLE WITH o-HALOGEN DERIVATIVES OF BENZOIC (OR NICOTINIC) ACID CHLORIDES

Edgars Abele, Kira Rubina, Tatjana Beresneva

Latvian Institute of Organic Synthesis, 21 Aizkraukles Street, Riga, LV-1006, Latvia,
E-mail: abele@osi.lv

ABSTRACT:
A simple one-flask method for the selective preparation of 2(-1H-imidazol-2-ylsulfanyl)benzoic or nicotinic acids directly from imidazole thiones and o-halogen derivatives of benzoic (or nicotinic) acid chlorides in the bicatalytic system solid Cs_2CO_3 / CuI / Bu_4NBr / DMF has been developed. Reactions of 2-(2-mercaptoimidazolyl)-benzoic (or nicotinic) acids with EDC (or $BrCH_2CH_2Br$) leads to imidazo[1,2-a][3,1]thiazin-5-ones as single cyclization products. Cu-catalyzed reactions of 2-aminobenzothiazoles with 2-iodobenzoic acid chloride chloride in the system Et_3N/ CuI / Phen (1,10-phenanthroline) / DMF afforded unknown 6a-chloro-6,6a-dihydro-7-thia-6,11b-diazabenzo[c]fluoren-5-ones as main products in yields up to 34%.

Keywords: copper catalysis, imidazol-2-thiones, 2(-1H-imidazol-2-ylsulfanyl)benzoic or nicotinic acids, 2-aminobenzothiazoles, 6a-chloro-6,6a-dihydro-7-thia-6,11b-diazabenzo[c]fluoren-5-ones

INTRODUCTION

Imidazothiazines and pyrimidothiazines are of great interest as biologically active compounds [I-III]. Common methods for the preparation of imidazothiazine ring systems were described in reviews [IV]. Among known methods for the preparation of imidazo[1,2-*a*][3,1]benzothiazine it is necessary to mention the thermal cyclization of 2-aminobenzothiazine pyruvate salts [V]. 2-[(Pentafluorophenyl)methylthio]benzimidazole undergoes cyclization to tetrafluorobenzimidazobenzothiazine in the presence of NaH in THF [VI]. 5*H*-Benzo[4,5][1,3]thiazino[2,3-*b*]quinazolin-12-one was obtained from 2-(2-hydroxymethylphenyl)-2-mercapto-3*H*-quinazolin-4-one in the presence of dry HCl / EtOH [VII]. Synthesis of different iimidazothiazinones by cyclization of 2-mercaptoimidazoles with o-halogen derivatives of benzoic (or nicotinic) acids (or acid chlorides) was also well documented [VIII]. However, direct formation of 2(-1H-imidazol-2-ylsulfanyl)benzoic or nicotinic acids in the above reactions was not observed. Synthesis of 2-(1H-benzoimidazol-2-ylsulfanyl)nicotinic acid was realized only by two step process from corresponding benzimidazole thione and 2-chloronicotinic acid chloride [IX]. Therefore the first aim of present work is elaboration of simple

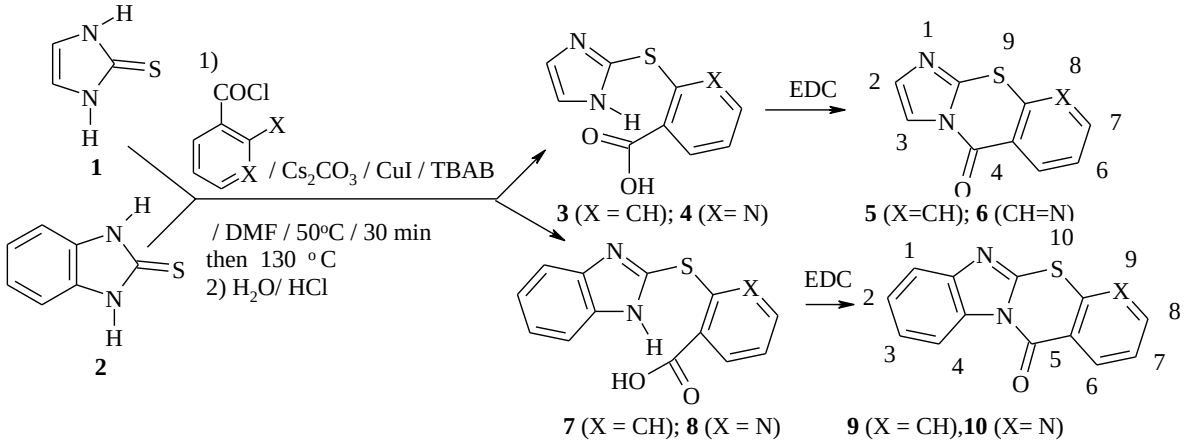
and convenient method for the preparation of novel 2(-1H-imidazol-2-ylsulfanyl)benzoic or nicotinic acids.

Recently Cu-catalyzed synthesis of benzo and pyridyl fused imidazo[2,1-*b*][1,3]thiazines, [1,2,4]triazolo[5,1-*b*][1,3]thiazines, and pyrimido[2,1-*b*][1,3]thiazin-6-ones have been demonstrated [X]. 5H-Benzothiazolo[3,2-a]quinazolin-5-ones were classically prepared by the thermal cyclization of pentafuorobenzoylaminobenzothiazoles [XI] or by the reaction of 2-aminobenzothiazole with o-fluorobenzoic acid chloride in the presence of triethylamine [XII]. The second aim of present work is investigation of selectivity of formation of products in the Cu-catalyzed reaction of 2-aminobenzothiazole and 2-amino-1-benzylbenzomidazole with 2-iodobenzoic acid chloride.

RESULTS AND DISCUSSION

Synthesis of 2(-1H-imidazol-2-ylsulfanyl)benzoic or nicotinic acids **3,4,7,8** were carried out from corresponding thiones **1** and **2** by one flask stepwise process (N-acylation, S-arylation and hydrolysis of amide group) in the bicatalytic system o-halogen derivatives of benzoic (or nicotinic) acid chlorides / solid Cs_2CO_3 / CuI / Bu_4NBr / DMF (Scheme 1). Interestingly, that the above reaction was highly selective and leads to acid derivatives **3, 4, 7, 8** in 26-92% yields. Interestingly, that the formation of imidazothiazine derivatives **5, 6, 9, 10** did not occurred in theses cases. However, the formation of compounds **5, 6, 9, 10** readily occurred from acids **3, 4, 7, 8** in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) in methylene chloride. Imidazothiazines **5, 6, 9, 10 w**ere isolated in 14-66% yields. The similar cyclization of 2(-1H-imidazol-2-ylsulfanyl)benzoic or nicotinic acids to polycycles **5, 6, 9, 10** was also realized in the system 1,2-dibromoethane (1 eq.) / solid K_2CO_3 (3 eq.) in refluxing acetone.

Scheme 1

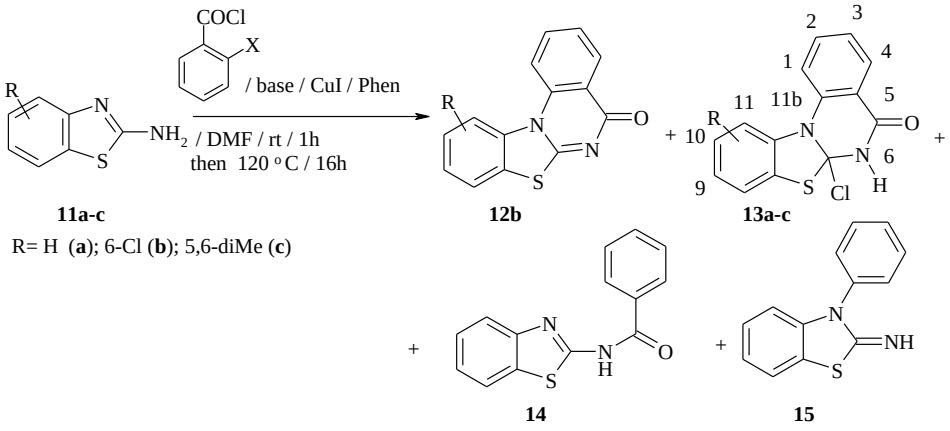


The influence of base on the Cu-catalyzed reaction of 2-aminobenzothiazole (**11a)** with 2-iodobenzoic acid chloride was studied in details. Surprisingly, the treatment of amine **11a** with 2-iodobenzoic acid chloride in the system Et_3N/ CuI / Phen (1,10-phenanthroline) / DMF leads to 2-benzoylaminobenzothiazole (**14**) as main product in 14% yield (Scheme 2, Table 1). The structure of compound **14,** which formed by dehalogenation of an intermediate 2-(2-iodobenzoylaminobenzothiazole in the presence of Cu-catalyst, was confirmed by X-ray data. Unstable 6a-chloro-6,6a-dihydro-7-thia-6,11b-diazabenzo[c]fluoren-5-one **(13a)** (yield 8%) was

isolated as minor product in the above reaction. Similar products **13b, c** were obtained using 6-chloro-2-aminobenzothiazole (**11b**) and 5,6-dimethyl-2-aminobenzothiazole (**11c**) as starting material. The formation of compounds **13a-c** included two steps. In the first step 2-aminobenzothiazole react with 2-iodobenzoic acid chloride leading to cyclization products (type **12b**). The next step of the reaction included addition of HCl to C=N double bond in the intermediates **12** leading to products **13a-c**. The source of HCl in these reactions was triethylamine hydrochloride (or DBU·HCl) formed during N-acylation of aminobenzothiazoles. Interestingly, that Cu-catalyzed reaction of amine **11a** with 2-iodobenzoic acid chloride in the presence of DBU afforded 3-phenyl-3H-benzothiazol-2-ylideneamine **(15)** (yield 44%) as main product. The mechanism of formation of compound **15** included N-acylation of compound **11a**, followed by Cu-catalyzed N-arylation and hydrolysis of amide group forming intermediate 3-(2-carboxyphenyl)-3H-benzothiazol-2-ylideneamine. Thermal decarboxylation of this intermediate afforded compound **15.**

Cu-catalyzed reaction of 2-amino-1-benzylbenzoimidazole (**16**) with 2-iodobenzoic acid leads to 7-benzyl-7H-6,7,11b-triazabenzo[c]fluoren-5-one (**17**) in 27% yield (Scheme 3).

Scheme 2



Scheme 3

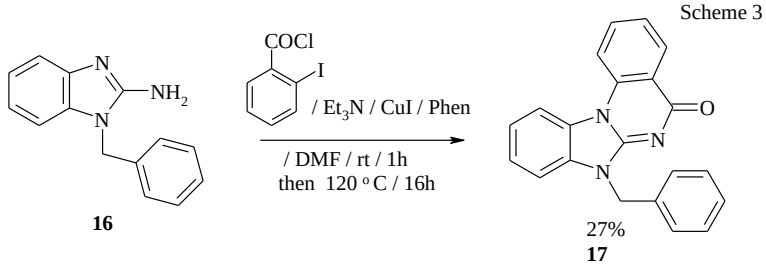


Table 1. Cu-catalyzed reactions of of 2-aminobenzothiazoles and 1-benzyl-2-aminobenzoimidazole with o-iodobenzoic acid chloride.

Starting compound, R	Base	Yield of products, %
H (**11a**)	Et_3N	8 (**13a**), 10 (**14**)
H (**11a**)	Cs_2CO_3	Traces
H (**11a**)	DBU	10 (**13a**), 44 (**15**)
6-Cl (**11b**)	Et_3N	14 (**12b**), 34 (**13b**)
5,6-diMe (**11c**)	Et_3N	22 (**13c**)

EXPERIMENTAL SECTION

^{1}H NMR spectra were registered on Varian Mercury BB 400 MHz in $CDCl_3$. Mass-spectra were recorded on Alliance Waters 2695 instrument with Full scan POS NEG 16 detector. Thiones **1-2,** 2-aminobenzothiazoles **11a-c,** 2-aminobenzoimidazole, o-iodobenzoic acid, 2-chloronicotinic acid, cesium carbonate (all Acros), copper (I) iodide, Bu_4NBr, 1,10-phenanthroline (Reahim), dimethylformamide (extra dry, over molecular sieves, Acros) and EDC (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide) (Aldrich) were used without purification. 1-Benzyl-2-aminobenzoimidazole (**16**) was prepared by benzylation of 2-aminobenzoimidazole as described in article [XIII]. o-Iodobenzoic acid chloride and 2-chloronicotinic acid chloride were obtained from thionyl chloride and o-iodobenzoic acid or 2-chloronicotinic acid, correspondingly.

General procedure for the reaction imidazole thiones 1 and 2 with o-halogen derivatives of benzoic (or nicotinic) acid chlorides.. Synthesis of 2(-1H-imidazol-2-ylsulfanyl)benzoic or nicotinic acids 3,4,7,8. Cs_2CO_3 (2.25 mmol) was added to the solution of imidazole thiones **1** or **2** (0.75 mmol), o-halogen derivatives of benzoic (or nicotinic) acid chlorides (0.75 mmol), CuI (0.030 g, 0.15 mmol) and Bu_4NBr (0.048 g, 0.15 mmol) in dry DMF (5 ml) in a glass reactor (50 ml) under argon. The reaction mixture was stirred at 50^{o}C for 0.5 h, then at 130^{o}C for 16h under argon. The solvent was removed under reduced pressure and crude residue was dissolved to water (5ml), and acidified to pH 5 by aq. HCl. The products were extracted with methylene chloride (3 x 20 ml). The solvent was removed under reduced pressure and crude residue was chromatographed on silica using CH_2Cl_2 : EtOH (from 1:0 to 5:1) as eluent.

2-(1H-Imidazol-2-ylsulfanyl)benzoic acid (3). Yield 92%. M.p.>200^{o}C. LC-MS, 221 (M^++1, 85), 203 (100). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.46 (1H, m, aromatic), 7,24 and 7.98 (2H, both m, imidazole protons), 7.24-7.37 (3H, m, aromatic).

2-(1H-Imidazol-2-ylsulfanyl)nicotinic acid (4). Yield 56%. M.p. >200^{o}C. LC-MS, 222 (M^++1, 85),. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.30 (1H, m, aromatic), 7.45 (1H, m, H-5 in pyridine), 7.68 (1H, m, aromatic), 7.95 (1H, m, aromatic), 8.09 (1H, m, aromatic), 8.17 (1H, m, H-4 in pyridine), 8.39 (1H, d, J = 7.6 Hz, H-6 in pyridine).

2-(1H-Benzoimidazol-2-ylsulfanyl)benzoic acid (7). Yield 33%. M.p. >200^{o}C. LC-MS, 271 (M^++1, 90), 242 (100). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.75 (1H, bs, NH), 7-18-7.23 (5H, m, aromatic), 7.85 (2H, m, H-7 in benzoimidazole and H-6 in benzoic acid).

2-(1H-Benzoimidazol-2-ylsulfanyl)nicotinic acid (8). Yield 26%. M.p. >200^{o}C. LC-MS: 272 (M^++1, 100). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.17–7.23 (3H, m, two aromatic and H-5 in pyridine), 7.53-7.55 (2H, m, aromatic), 8.16-8.30 (2H, m, H-4 and H-6 in pyridine).

General procedure for the reaction of 2-(1H-imidazol-2-ylsulfanyl)benzoic or nicotinic acids 3,4,7,8 with EDC. The solution of 2-(1H-imidazol-2-ylsulfanyl)benzoic or nicotinic acids **3,4,7** or **8** (0.37 mmol), EDC (0.08g, 0.41 mmol) in dry methylene chloride (10 ml) in a glass reactor (50 ml) under argon. The reaction mixture was stirred at room temperature for 18 h, solvent was removed under reduced pressure and crude residue was chromatographed on silica using hexane : ethyl acetate (from 2:1 to 1:1) as eluent to obtain compounds **5, 6, 9, 10**.

.**9-Thia-1,3a-diazacyclopenta[b]naphthalene-4-one (5).** Yield 66%. M.p. 138-140^{o}C. LC-MS: 203 (M^++1, 100). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.37 and 8.06 (2H, d, J = 2.2 Hz, imidazole protons), 7.50-7.75 (3H, m, aromatic), 8.60 (1H, d, J = 8.0 Hz, aromatic).

.**9-Thia-1,3a,8-triazacyclopenta[b]naphthalene-4-one (6).** Yield 14%. M.p. 163-165^{o}C. LC-MS: 204 (M^++1, 100). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.41 and 8.09 (2H, d, J = 2.2 Hz,

imidazole protons), 7.49 (1H, dd, J_1 = 8.2 Hz, J_2 = 6.0 Hz, H-6), 8.80-8.85 (2H, m. H-5 and H-7).

10-Thia-4b,11-diazabenzo[b]fluoren-5-one (9). Yield 65%. M.p. 188-189°C. LC-MS: 253 (M^++1, 100). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.46–7.56 (4H, m, H-2, H-3, H-7 and H-8), 7.80, 8.56 and 8.87 (4H, m, H-1, H-4, H-6, H-9).

10-Thia-4b,9,11-triazabenzo[b]fluoren-5-one (10). Yield 30%. M.p. 190-191°C. LC-MS: 254 (M^++1, 100). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.46–7.56 and 7.77-7.83 (4H, both m, H-1, H-2, H-3, H-7), 8.57-8.62 and 8.83-8.89 (3H, both m, H-4, H-6 and H-8).

General procedure for the reaction of 2-aminobenzothiazoles (11a-c) and 2-amino-1-benzylbenzoimidazole 16 with o-iodobenzoyl chloride. Base (3 mmol) was added to the solution of 2-aminobenzothiazoles **11a-c** or 2-amino-1-benzylbenzoimidazole **(16)** (1 mmol) and 2-iodobenzoic acid chloride (0.266 g, 1 mmol), CuI (0.038 g, 0.2 mmol) and 1,10-phenanthroline (0.040g, 0.2 mmol) in dry DMF (3 ml) in a glass reactor (50 ml) under argon. The reaction mixture was stirred at room temperature for 1h, then 120 °C for 16h under argon. The solvent was removed under reduced pressure and crude residue was chromatographed on silica using hexane : ethyl acetate (from 4:1 to 0:1) as eluent.

2-Benzylaminobenzothiazole (14) [XIV]**.** Oil. LC-MS, 254 (M^++1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.34 (1H, t, J = 7.6 Hz, benzothiazole proton), 7.47 (1H, t, J = 7.6 Hz, benzothiazole proton), 7.57 (2H, t, J = 8.0 Hz, H-3 and H-5 in Ph), 7.65 (1H, m, H-4 in Ph), 7.78 and 8.02 (4H, both d, J = 8.0 Hz, H-4 and H-7 in benzothiazole), 8.14 (2H, d, J = 7.6 Hz, H-2 and H-6 in Ph).

6a-Chloro-6,6a-dihydro-7-thia-6,11b-diazabenzo[c]fluoren-5-one (13a). M.p. 40-45°C (dec). LC-MS, 289 (M^++,100), 150 (35). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.35 (1H, t, J = 8.0 Hz, aromatic), 7.47 (1H, t, J = 8.0 Hz, aromatic), 7.49 (1H, t, J =7.6 Hz, aromatic), 7.57 (1H, t, J = 8Hz, aromatic), 7.61 (1H, d, J = 8.0 Hz, aromatic), 7.70 (1H, d, J = 7.6 Hz, aromatic), 7.81 (1H, d, J = 8.0 Hz, aromatic), 8.03 (1H, d, J = 8.0 Hz, aromatic).

3-Phenyl-3H-benzothiazol-2-ylideneamine (15). Spectroscopic data are identical with those described in the literature [XV].

6a,9-Dichloro-9,10-dimethyl-6,6a-dihydro-7-thia-6,11b-diazabenzo[c]fluoren-5-one (13b). M.p. 40-45°C. GC-MS: 323 (M^+, 11), 287.0 (13), 139.0 (100), 111.0 (32), 75.0 (12). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.47-7.51 and 7.55-7.63 (4H, both m, aromatic), 7.70 and 7.78 (2H, both d, J = 7.6 Hz, H-4 and H-11), 8.18 (1H, d, J = 0.5 Hz, H-8).

6a-Chloro-9,10-dimethyl-6,6a-dihydro-7-thia-6,11b-diazabenzo[c]fluoren-5-one (13c). Oil (decomposes during hours). GC-MS: 316.1 (M^+, 24), 281.1 (26), 253.0 14), 139.0 (100), 111.0 (33).

7-Benzyl-7H-6,7,11b-triazabenzo[c]fluoren-5-one (17). Oil. GC-MS: 325.1 (M^+, 43), 234.0 (10), 91.0 (100), 77.1 (7). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.43 (2H, s, CH_2), 7.11-7.56 (11H, m, aromatic), 7.79 (1H, m, H-2), 8.28 (1H, d, J = 8.4 Hz, H-4).

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