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New Route to 3-Alkylthiazolo[3,2-a]benzimidazole Derivatives

Christian Roussel *, Federico Andreoli, Mihaela Roman, Maria Hristova and Nicolas Vanthuyne

UMR "Chirotechnologies: Catalyse et Biocatalyse", Université Paul Cézanne Aix-Marseille III, 13397 Marseille CEDEX 20 France.

* Author to whom correspondence should be addressed. E-mail: Christian.roussel@univ.u-3mrs.fr

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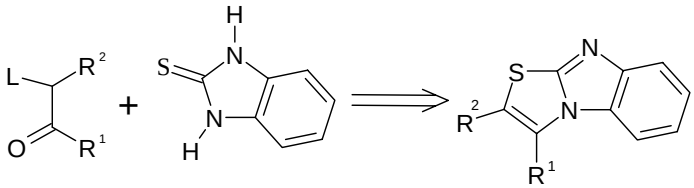
Abstract: 3-Alkyl-thiazolo[3,2-a]benzimidazole derivatives are obtained in high yields via the corresponding 4-alkyl-*N*-3-(2-aminophenyl)-thiazoline-2-thiones which are easily prepared from 1,2-diaminobenzene, CS_2 and halogenoketones. This new route compares advantageously with the classical mercaptobenzimidazole routes in term of simplicity, isolated yields and availability of the starting materials.

Keywords: 2-Methylthiothiazolium salts, fused heterocycles, ring closure.

Introduction

3-Methyl-thiazolo[3,2-a]benzimidazole (**1a**) is available for screening purposes in three libraries according to Chem. Abstracts. So far the reported synthetic routes leading to thiazolo[3,2-a]benzimidazole skeleton begin from the preformed 2-mercaptobenzimidazole which is condensed at the mercapto-group with various electrophiles such as alpha-haloketones [1], propargyl halides [2] or 1,2,3-tribromopropane [3] followed by cyclization to form the thiazole ring in the last step (Scheme 1).

Scheme 1

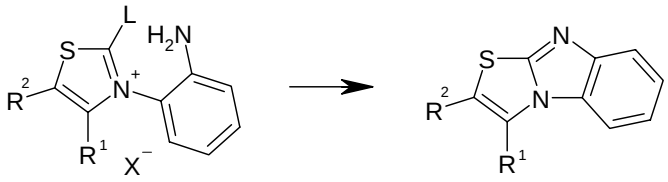


A variation involved the reaction of enol ester which acts as nucleophile on the S-S dimer of mercaptobenzimidazole which acts as an electrophile [4]. The enol ester and the dimer were prepared in situ and this “umpolung” reactivity resulted in the same sequence of bond formation as before. We report herein a new synthesis starting from a preformed thiazolium salts.

Results and Discussion

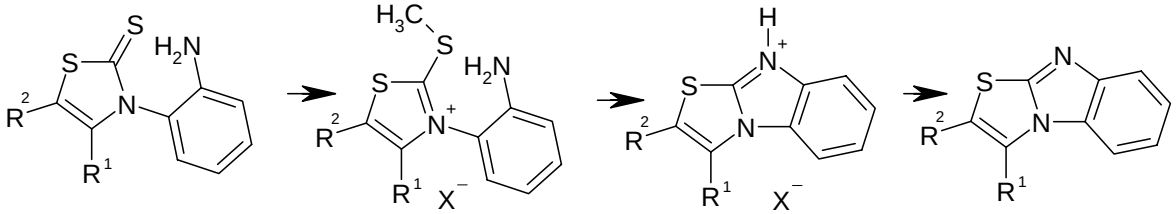
Curiously enough, the reaction sequence in which the C=N bond is formed in the last step from preformed activated thiazole ring has never been attempted to the best of our knowledge. The leaving group in position 2 of thiazolium salt will be expelled during cyclization. This approach is depicted in Scheme 2.

Scheme 2



Among the possible leaving groups in position 2 of the thiazolium salts, the methylthio group was particularly attractive since it could be easily generated by methylation at sulphur of the parent thiazoline-2-thione derivative. (Scheme 3)

Scheme 3



4a R^1=Me, R^2=H
4b R^1=Me, R^2=Me
4c R^1=tert-Bu, R^2=H

3a R^1=Me, R^2=H
3b R^1=Me, R^2=Me
3c R^1=tert-Bu, R^2=H

2a R^1=Me, R^2=H
2b R^1=Me, R^2=Me
2c R^1=tert-Bu, R^2=H

1a R^1=Me, R^2=H
1b R^1=Me, R^2=Me
1c R^1=tert-Bu, R^2=H

N-(2-Aminophenyl)-4-methyl-thiazoline-2-thione (**4a**) has been first described in 1998 [5]. This compound attracted our attention due to our long standing interest in the atropisomers of N-arylthiazoline-2-thione derivatives in terms of barriers to racemization and chiral recognition mechanisms on chiral stationary phases [6-10]. Compound **4a** is readily available in high yield by reacting chloroacetone in CH_3CN with the dithiocarbamate obtained quantitatively from 1,2-diamino-benzene and CS_2 in the presence of triethylamine [5]. In our hands, the isolated yield in recrystallized thiazoline-2-thione derivative was 64%. The thiazolinethione reaction with iodomethane in anhydrous

acetone at rt afforded the thiazolium salt **3a** ($X^-=I^-$ in Scheme 2 and Scheme 3) in quantitative yield. The reaction was monitored by TLC until the total disappearance of the starting thiazoline-thione was confirmed. As expected, due to the very high nucleophilicity of the sulphur atom, no methylation occurred on the amino group. After evaporation of acetone and methyl iodide in excess, NMR data were recorded on the crude reaction medium without any attempts to isolate the thiazolium salts. In the same reactor, the crude thiazolium salt when refluxed in methanol eliminated MeSH to yield 3-methyl-thiazolo[3,2-a]benzimidazolium iodide (**2a**) as a single compound after evaporation of the solvent. NMR data of this crude reaction mixture were recorded again to check the disappearance of the S-Me signal and the appearance of the protonated thiazolobenzimidazole **2a**. It may prove of interest to obtain directly the iodide salt. More generally, in the reaction sequence we are reporting, the counter anion is coming from the methylating agent and thus a wide variety of 3-methyl-thiazolo[3,2-a]benzimidazolium salts differing by the associated anion could be directly obtained. It must be stressed that obtaining pure isolated and recrystallized iodide salts was not our goal and thus no further analysis were performed on the crude iodide salts. The free 3-methyl-thiazolo[3,2-a]benzimidazole (**1a**) is easily obtained in pure state by treatment with aqueous $NaHCO_3$ followed by careful extraction in CH_2Cl_2. In the starting thiazoline-2-thione derivative **4a** the aryl group and the heterocycle are situated in two perpendicular planes giving rise to stable atropisomers [11], it results from this spatial arrangement that in the ^{1}H-NMR spectrum the 4-methyl group is highly shielded (δ = 1.93 ppm), whereas in the final product **1a** the methyl group is highly deshielded due to the planarity of the structure (δ = 2.70 ppm). In the two non-isolated thiazolium and thiazolo[3,2-a]benzimidazolium iodide intermediates, the chemical shifts of the proton of that particular methyl group appeared at 2.25 ppm and 2.92 ppm respectively. The reaction sequence was also exemplified with success to yield **1b** starting from the already described N-(2-aminophenyl)-4,5-dimethyl-thiazoline-2-thione (**4b**) [12].

It was of interest to check the robustness of the reaction sequence in case of strong steric repulsion between the substituent in position 4 of the thiazolium salts and the aryl group, which shall adopt a coplanar arrangement in the final product. We prepared the corresponding analogues starting from chloropinacolone to obtain the 3-*tert*-butyl-thiazolo[3,2-a]benzimidazole (**1c**). The cyclization rate is slower than in the case of the 3-methyl analogues leading to **1a** or **1b**. After 12 hours reflux in methanol the mixture is composed of 16% of the unchanged thiazolium salt (**3c**) and 84% of 3-tert-butyl-thiazolo[3,2-a]benzimidazolium iodide **2c**. However, the transformation is quantitatively achieved after 41 hrs without the formation of any by-product.

Conclusions

The thiazolium route we have exemplified for the first time, compares advantageously to the mercaptobenzimidazole routes in term of simplicity, isolated yield and availability of the starting materials.

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Experimental

General

^{1}H-NMR spectra were recorded at 300 or 200 MHz and ^{13}C-NMR spectra at 75 or 50 MHz on Bruker Avance DPX-300 or 200 instruments. Chemical shifts are reported in ppm with the signal for residual solvent as internal standard. *J* values are reported in Hz. Melting points were measured using a Kofler hot stage apparatus and are not corrected. Flash column chromatography was performed with silica gel 60 (230-400 mesh). TLC were carried out on Merck 60F_{254} silica plates.

N-(2-Aminophenyl)-4-methyl-thiazoline-2-thione (**4a**)**.**

The already reported synthesis of **4a** [5], has been used with very slight modifications. Triethylamine (68.6 mL, 492 mmol) was added to a suspension of 1,2-phenylenediamine (28 g, 259 mmol) in CS_2 (600 mL). After stirring for 2 h, the dithiocarbamate salt was filtered off, washed with Et_2O and used without further purification. 1-Chloro-propan-2-one (20 mL, 251 mmol) was added to a suspension of 70 g (245 mmol) of dithiocarbamate salt in 600 mL of acetonitrile. After stirring for 12-48 h at r.t., the solvent was removed *in vacuo* and 66 mL of 36% HCl was added and the mixture was left under stirring for 20 min. Water (400 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 400 mL). The organic phase was washed with water (3 x 200 mL), dried over $MgSO_4$ and evaporated. Recrystallisation in absolute ethanol afforded (**4a**, 35 g, 64 %) as a white powder with m.p. 180°C (lit.[5]: 184°C); Rf 0.22 (CH_2Cl_2). The ^{1}H-NMR ($CDCl_3$, 300 MHz) and ^{13}C-NMR ($CDCl_3$, 75 MHz) were in agreement with literature data for this compound [5].

N-(2-Aminophenyl)-4, 5-dimethyl-thiazoline-2-thione (**4b**).

The same procedure as for **4a** was used with 3-chloro-butan-2-one (2.45 mL, 24.2 mmol) to afford **4b** (5.2 g, 73 %) as a white powder upon recrystallisation in ethanol 96%. In this case, HCl was replaced by H_2SO_4 [5, 12]. White powder with m.p. 149°C (lit.[5,12]: 139-140°C); Rf 0.20 (CH_2Cl_2). The ^{1}H-NMR ($CDCl_3$, 300 MHz) and ^{13}C-NMR ($CDCl_3$, 75 MHz) were in agreement with literature data for this compound [5,12].

N-(2-aminophenyl)-4-tert-butyl-thiazoline-2-thione (**4c**).

The same procedure as for **4a** was used with 1,2-phenylenediamine (1 g, 9.2 mmol) and 1-chloro-pinacolone (1.21 mL, 9.2 mmol) to afford, after column chromatography on silica gel with CH_2Cl_2 elution, **4c** (0.8 g, 44%) as a crystalline white powder with m.p. 190°C; Rf 0.42 (CH_2Cl_2); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 1.17 (s, 9H, CH_3), 3.62 (s, 2H, NH_2), 6.41 (s, 1H, =CH), 6.80-7.40 (m, 4H, Ar); ^{13}C-NMR ($CDCl_3$, 50 MHz): δ = 29.48 (CH_3), 34.74 (C-(CH_3)$_3$), 106.08 (=CH), 117.37, 118.83, 125.68, 130.55, 131.00, 144.04, 153.45, 190.91 (C=S); Anal. For $C_{13}H_{16}N_2S_2$: calcd. C 59.05, H 6.10, N 10.59, S, 24.25; found C 59.04, H 6.23, N 10.58, S 24.50.

General Procedure for the synthesis of the thiazolo[3,2-a]benzimidazole (**1a, 1b, 1c**).

N-(2-Aminophenyl)-thiazoline-2-thione (2.25 mmol) and CH_3I (1.4 mL, 10 eq) were stirred in 10 mL of acetone at r.t. for 3 h. Evaporation of the excess of CH_3I and acetone afforded quantitatively the thiazolium iodide. NMR and TLC were taken on the crude reaction medium to check the completeness of the methylation. (NMR data shown). In the same vessel, crude 2-methylthio-N-(2-aminophenyl)-thiazolium iodides (2.25 mmol) were refluxed in 20 mL of methanol for 12 h (41 h for the *tert*-Bu-derivative). Evaporation of the methanol afforded quantitatively the thiazolo[3,2-a]benzimidazolium iodides (NMR data shown). To these crude solids, 20 mL of a saturated $NaHCO_3$ solution was added and the solution was extracted with CH_2Cl_2 (3 x 10 mL). The organic phase was dried over $MgSO_4$ and evaporated to afford quantitatively the thiazolo[3,2-a]benzimidazole derivatives.

3-Methyl-thiazolo[3,2-a]benzimidazole (**1a**)**.**

Pale yellow powder m.p. 162°C (lit.[1]160-165°C); Rf 0.45 (CH_2Cl_2/AcOEt 9/1). NMR data are consistent with literature data [1]. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 2.70 (d, 3H, CH_3, J = 1.2), 6.31 (q, 1H, =CH, J = 1.2), 7.10-7.40 (m, 2H, Ar), 7.70-7.85 (m, 2H, Ar); ^{13}C-NMR ($CDCl_3$, 50 MHz): δ = 14.33 (CH_3), 104.46 (=CH), 110.31, 119.04, 120.47, 123.06, 129.75, 130.23, 157.15(C=N).

2,3-Dimethyl-thiazolo[3,2-a]benzimidazole (**1b**).

White powder m.p. 151°C (lit. [1c] 154-156°C); Rf 0.45 (CH_2Cl_2/AcOEt 9/1). NMR data are consistent with literature data [1c]. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 2.19 (q, 3H, CH_3, J = 6.0), 2.43 (q, 3H, CH_3, J = 6.0), 7.00-7.30 (m, 2H, Ar), 7.50-7.70 (m, 2H, Ar); ^{13}C-NMR ($CDCl_3$, 50 MHz): δ = 11.52, 12.36, 110.15, 116.03, 118.88, 120.27, 122.67, 124.47, 130.31, 147.82, 155.00.

3-tert-Butyl-thiazolo[3,2-a]benzimidazole (**1c**).

Colorless oil; Rf 0.70 (CH_2Cl_2/AcOEt 9/1); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 1.61 (s, 9H, CH_3), 6.41 (s, 1H, =CH), 7.20-7.50 (m, 2H, Ar), 7.80-7.90 (m, 1H, Ar), 7.95-8.05 (m, 1H, Ar); ^{13}C-NMR ($CDCl_3$, 50 MHz): δ = 28.40, 33.44, 102.79, 113.90, 119.24, 120.28, 122.95, 130.06, 143.74, 148.92, 158.65; Anal. For $C_{13}H_{14}N_2S$: Calcd. C 67.79, H 6.13, N 12.16, S 13.92; found C 67.76, H 6.31, N 11.85, S 14.17.

NMR reference data for the non- isolated thiazolium and thiazolo-benzimadazolium iodide intermediates.

2-Methylthio-N-(2-aminophenyl)-4-methyl-thiazolium iodide (**3a**),

^{1}H-NMR (CD_3OD, 200 MHz): δ = 2.25 (d, 3H, CH_3, J = 1.1), 2.93 (s, 3H, S-CH_3), 6.75-7.45 (m, 4H, Ar) , 7.84 (q, 1H, =CH, J = 1.1); ^{13}C-NMR (CD_3OD, 50 MHz): δ = 13.87 (CH_3), 18.13 (S-CH_3), 118.03, 118.78, 118.94, 119.68, 128.41, 134.15, 145.26, 148.17, 181.66 (C-S).

2-Methylthio-N-(2-aminophenyl)-4,5-dimethyl- thiazolium iodide (**3b**).

^{1}H-NMR (CD_3OD, 300 MHz): δ = 2.14 (q, 3H, CH_3, J = 0.6), 2.56 (q, 3H, CH_3, J = 0.6), 2.90 (s, 3H, S-CH_3), 6.80-7.40 (m, 4H, Ar); ^{13}C-NMR (CD_3OD, 50 MHz): δ = 12.12 (=C-CH_3), 12.81(=C-CH_3), 18.37(S-CH_3), 118.61, 118.80, 120.36, 128.48, 130.26, 134.00, 143.64, 145.10, 177.73 (C-S).

2-Methylthio-N-(2-aminophenyl)-4-tert-butyl- thiazolium iodide (**3c**).

^{1}H-NMR (CD_3OD, 200 MHz): δ = 1.32 (s, 9H, CH_3), 2.88 (s, 3H, S-CH_3), 6.70-7.50 (m, 4H, Ar) , 7.85 (s, 1H, =CH); ^{13}C-NMR (CD_3OD, 50 MHz): δ = 18.13 (S-CH_3), 29.84 (3C, CH_3), 36.49 (C-$(CH_3)_3$), 117.84, 118.03, 118.61, 120.92, 130.24, 134.28, 145.89, 159.80, 184.37 (C-S).

3-Methyl-thiazolo[3,2-a]benzimidazolium iodide (**2a**)

^{1}H-NMR (CD_3OD, 300 MHz): δ = 2.92 (d, 3H, CH_3, J = 1.2), 7.26 (q, 1H, =CH, J = 1.2), 7.55-7.75 (m, 2H, Ar) , 7.80-7.90 (m, 1H, Ar) , 8.15-8.25 (m, 1H, Ar); ^{13}C-NMR (CD_3OD, 75 MHz): δ = 14.21, 112.02, 114.37, 115.50, 125.58, 128.03, 129.20, 134.32, 138.14, 155.85.

2,3-Dimethyl-thiazolo[3,2-a]benzimidazolium iodide (**2b**)

^{1}H-NMR (CD_3OD, 200 MHz): δ = 2.56 (q, 3H, CH_3, J = 1.0), 2.84 (q, 3H, CH_3, J = 1.0), 7.50-7.95 (m, 3H, Ar), 8.20-8.30 (m, 1H, Ar); ^{13}C-NMR (CD_3OD, 50 MHz): δ = 12.18 (CH_3), 12.38 (CH_3), 114.06, 115.61, 123.30, 125.21, 127.54, 129.26, 138.23, 153.25 (C=N).

3-tert-Butyl-thiazolo[3,2-a]benzimidazolium iodide (**2c**)

^{1}H-NMR (CD_3OD, 200 MHz): δ = 1.67 (s, 9H, CH_3), 7.25 (s, H, =CH), 7.50-7.70 (m, 2H, Ar), 7.80-7.95 (m, 1H, Ar), 8.25-8.35 (m, 1H, Ar); ^{13}C-NMR (CD_3OD, 50 MHz): δ = 28.98, 34.75, 110.16, 116.26, 117.19, 124.93, 127.45, 129.43, 139.99, 146.94, 157.96.

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11. These atropisomers are nicely separated by chiral HPLC on CHIRALCEL OD-H, mobile phase hexane / ethanol (50/50), 1 mL/min, 25°C, detection UV 254 nm and on-line polarimeter Jasco OR-1590, retention times Rt in minutes, retention factor $k = (Rt - Rt_0) / Rt_0$, selectivity factor α and resolution Rs are reported below : (**4a**) Rt(+) = 4.72 , Rt(-) = 5.82, k(+) = 0.52, k(-) = 0.88, α = 1.68 and Rs = 3.05.; (**4b**) Rt(+) = 4.59 , Rt(-) = 6.52, k(+) = 0.48, k(-) = 1.10, α = 2.29 and Rs = 4.87.; (**4c**) Rt(+) = 4.51 , Rt(-) = 6.17, k(+) = 0.45, k(-) = 0.99, α = 2.18 and Rs = 4.25.
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Samples Availability: Available from the authors.