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A new photocyclization approach to the rare 1,3-thiazino[6,5-*b*]indol-4-one derivatives

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Abstract—The analogs of indole phytoalexin cyclobrassinon have been prepared in four steps from corresponding 1-substituted 2-chloroindole-3-carboxylic acids, employing a hitherto unknown photochemical cyclization of new indolyl thiocarbamates to 1,3-thiazino[6,5-*b*]indole-4-one derivatives as a key step. © 2001 Elsevier Science Ltd. All rights reserved.

1,3-Thiazinoindoles represent an interesting group of heterocyclic compounds, because of their unusual chemical structure and interesting biological properties. There are four possible types (A–D) of ring fusion of indole at the bond *b* and 1,3-thiazine ring or its hydrogenated forms (Fig. 1).

The compounds of Type A, possessing a 1,3-thiazino[5,4-*b*]indole ring system, were prepared for the first time by treatment of 3-aminoindole with carbon disulfide in ethanol.[1] When *N*′-alkyl- or *N*′-aryl-*N*-3[(2-ethoxycarbonylindolyl)]thioureas were heated with polyphosphoric acid, 1,3-thiazino[5,4-*b*]indol-4-one derivatives with interesting serine protease inhibitory activity were obtained.[2] The compounds of Type B, 1,3-thiazino[6,5-*b*]indoles, **3**–**7**, are the indole phytoalexins, isolated from plants of the family *Cruciferae*.[3,4] (See Fig. 2.)

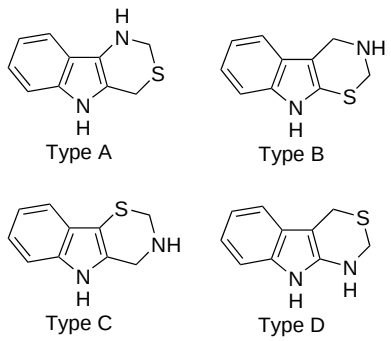
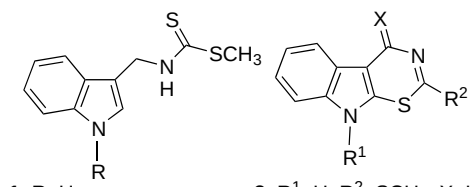


Figure 1.

Cyclobrassinin (**3**) was prepared by cyclization of brassinin (**1**) with pyridinium tribromide,[5,6] or *N*-bromosuccinimide.[7] Sinalbin B (**5**) has been synthesized analogously, by cyclization of 1-methoxybrassinin (**2**) with *N*-bromosuccinimide.[4] The subsequent oxidation of **5** with 3-chloroperoxybenzoic acid afforded sinalbin A (**6**).[4] Very recently, cyclobrassinon (**7**) has been synthesized in six steps from 2-chloroindole-3-carboxaldehyde.[8] The biological screening, performed with cyclobrassinin disclosed its antifungal,[9] phytotoxic[10] and canceroprotective[7,11] activity. The 1,3-thiazino[6,5-*b*]indole skeleton was also prepared by heating 2-chloroindole-3-carboxaldehyde with thiourea in ethanol.[12] Derivatives of Types C and D have not been described to date.



1, R=H
2, R=OCH_3

3, R^1=H, R^2=SCH_3, X=H, H
4, R^1=H, R^2=$SOCH_3$, X=H, H
5, R^1=OCH_3, R^2=SCH_3, X=H, H
6, R^1=OCH_3, R^2=$SOCH_3$, X=H, H
7, R^1=H, R^2=OCH_3, X=O

Figure 2.

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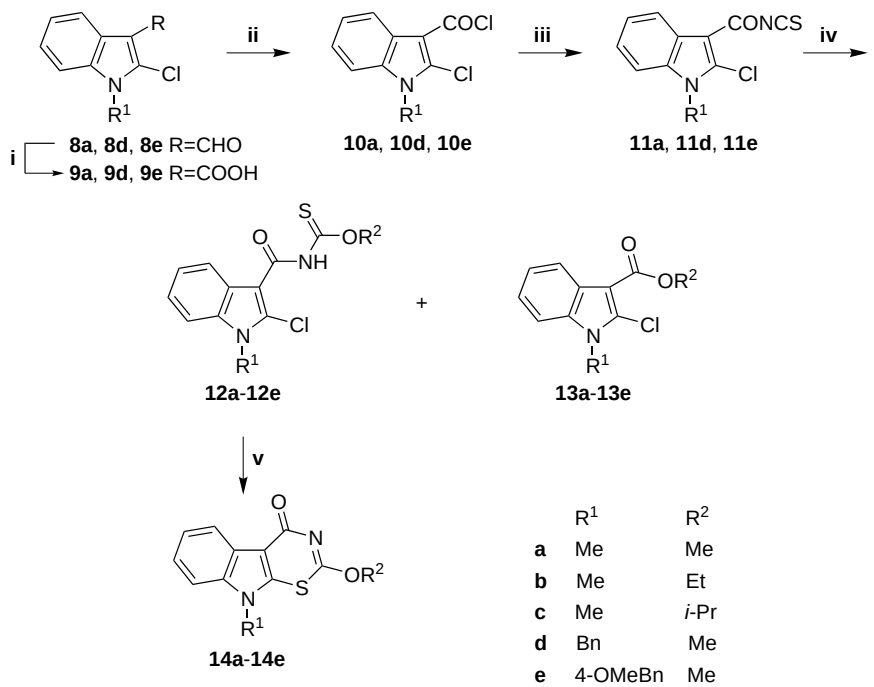
With respect to our continuing interest in the synthesis of indole phytoalexins and their analogs,[8,13,14] we have also decided to prepare 9-methyl cyclobrassinon **14a**, the close analog of indole phytoalexin cyclobrassinon (**7**). 1-Methyl-2-chloroindole-3-carboxaldehyde (**8a**,[15a] Scheme 1) was selected as a suitable starting compound. Its oxidation[16] with $KMnO_4$, according to a literature procedure,[15a] afforded 1-methyl-2-chloroindole-3-carboxylic acid (**9a**). Heating the acid **9a** with phosphorus trichloride in dry benzene (85–90°C) gave the unstable acid chloride **10a**, which, without further purification, was treated with KSCN with the formation of the stable isothiocyanate **11a**. Compound **11a** can be isolated by column chromatography as a crystalline compound, however with significant loss caused by decomposition on silica gel (red column).

Therefore, in the next reaction with methanol crude isothiocyanate **11a** was used. Heating **11a** with methanol (60°C) afforded the key intermediate, thiocarbamate **12a** accompanied by a side product, methyl 1-methyl-2-chloroindole-3-carboxylate (**13a**, Scheme 1). The formation of **13a** can be explained via the thiocyanate anion splitting, facilitated by the electron-donating methyl group, with the formation of a reactive ketene, which immediately reacts with methanol.[17] The direct methanolysis of **11a** is less probable, since the reaction of methanol with 1-Boc-2-chloroindole-3-ylcarbonylisothiocyanate[8] did not afford an analogous side product. Thiocarbamate **12a** was separated from the reaction mixture by simple crystallization from acetone/cyclohexane.

It was recently shown[8] that thiocarbamates of type **12**, possessing the activating electron-withdrawing Boc-group on the indole nitrogen, readily undergo nucleophilic intramolecular substitution of a chlorine atom with sulfur under very mild conditions (Et_3N, rt). Many attempts to cyclize thiocarbamate **12a** under the action of various bases (for example Et_3N, NaH, MeONa) and with temperatures up to 150°C resulted in the formation of decomposition products and no cyclization took place. Another possibility for substitution of chlorine is the weakening of the carbon–chlorine bond by photochemical excitation. Despite several examples of nucleophilic substitutions of the chlorine atom with sulfur in the 2-position of indole,[12,18–20] the photochemical approach has not been applied for this purpose.[21] A methanolic solution of thiocarbamate **12a** (long wave absorption maximum λ_{max} 308 nm, ε 1850) was irradiated using a high pressure mercury lamp through a Pyrex filter under a nitrogen atmosphere. Due to the decomposition of the product caused by liberated HCl, the addition of Et_3N to the reaction mixture was necessary. Since the thiazinoindole **14a** formed appeared to be photolabile, the reaction time was optimized and the reaction was stopped, before all the starting material was consumed. The product, 2-methoxy-9-methyl-1,3-thiazino[6,5-*b*]indol-4-one (**14a**, Scheme 1) was isolated by column chromatography.

The elaborated method of intramolecular photochemical substitution of a chlorine atom by sulfur was successfully applied to the synthesis of thiazinoindoles



Scheme 1. *Reagents and conditions*: (i) $KMnO_4$, **9a**,[15a] **9d**,[15b] **9e**: acetone/water, rt, 65%; (ii) PCl_3, benzene, 85–90°C, **a**: 35 min, **d**: 30 min, **e**: 1 h; (iii) KSCN, acetone, rt, **a**: 20 min, 30%, **d**: 1 h, 40%, **e**: 1 h, 29%, the yields of isolated isothiocyanates are based on carboxylic acids **8**; (iv) MeOH, 60°C, 1 h, 26% (**12a**), 18% (**13a**); EtOH, 60°C, 1 h, 23% (**12b**), 8% (**13b**); *i*-PrOH, 60°C, 2 h, 21% (**12c**), 19% (**13c**); MeOH, 60°C, 1 h, 42% (**12d**), 2% (**13d**); MeOH, 60°C, 1 h, 40% (**12e**), 10% (**13e**), for **12** and **13** yields are based on carboxylic acids **8**, using the crude isothiocyanates **11**; (v) *hv*, Pyrex filter, N_2, Et_3N, methanol, rt, **a**: 35 min, 33%, **b**: 75 min, 38%, **c**: 35 min, 55%, **d**: 35 min, 47%; **e**: 35 min, 40%.

14b–**14e** by cyclization of thiocarbamates **12b**–**12e** in 37–55% yield. The biological activity of the synthesized compounds and experimental details for the synthesis of further analogs will be published elsewhere.

Experimental procedure for photocyclization: To a stirred solution of thiocarbamate **12a**–**12e** (1 mmol) in methanol (200 ml) was added triethylamine (0.202 g, 0.28 ml, 2 mmol) and the mixture was irradiated (high pressure mercury lamp, Tesla RVK-125) through a Pyrex filter in a water-cooled immersed apparatus for 35 min (**12a**, **12c**–**12e**) or 75 min (**12b**). Nitrogen gas was bubbled through the solution for 15 min before irradiation and during the reaction. After evaporation of the methanol, the residue was dissolved in chloroform (5 ml) and chromatographed on 50 g of silica gel (benzene/acetone 7:1). The eluate was evaporated and thiazinoindoles **14a**–**14e** were crystallized from an appropriate solvent (**14a**, **14b**–**14c** acetone/cyclohexane; **14d** and **14e** dichloromethane/hexane).

Spectral data for 9-methylcyclobrassinon (14a): Yield 33%, mp 202–205°C. IR ($CHCl_3$, cm^{-1}): 1580 and 1650 (C=N-C=O). ^1H NMR (500 MHz, $CDCl_3$, δ, ppm): 3.69 (s, 3H, NCH_3); 4.17 (s, 3H, OCH_3); 7.13–7.50 (m, 3H, $H_{arom.}$); 8.25–8.55 (m, 1H, $H_{arom.}$). ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 30.72 (NCH_3), 57.68 (OCH_3), 102.70 (C), 108.58 (CH), 121.79 (CH), 122.50 (CH), 124.06 (CH), 125.07 (C), 138.27 (C), 139.49 (C), 164.54 and 166.42 (C=N-C=O). EIMS: [70 eV, m/z (%)]: 246 (M^+, 61), 189 (100), 160 (15), 117 (25), 89 (10). Anal. calcd for $C_{12}H_{10}N_2O_2S$: C, 58.52; H, 4.09; N, 11.37. Found: C, 58.37; H, 3.88, N, 11.52.

Acknowledgements

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