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AN EFFICIENT SYNTHESIS OF CAMALEXIN ANALOGOUS

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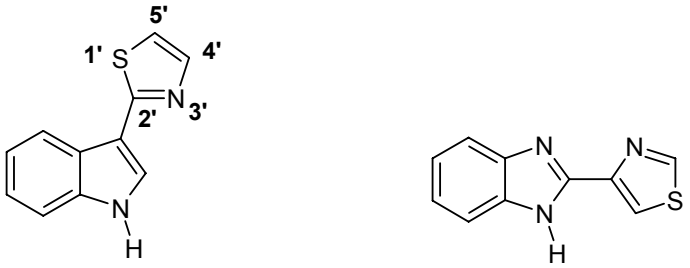
Abstract: A convenient method for the synthesis of 3-thiazolylindoles has been proposed. This synthesis is based on the condensation of bromoacetylindole with thioureas.

Keywords: *indoles, thiazolylindole, thiourea, camalexin*

INTRODUCTION

Camalexin (fig.1) is a natural phytoalexin, produced in the leaves of *Camelina sativa* in response to infection by the fungus *Alternaria brassicae* [1]. Camalexin is also the principal phytoalexin found in *Arabidopsis thaliana* [2]. It exhibits antifungal activity similar to the systemic fungicide thiabendazole [1, 3] (fig. 1) and also has antitumoral activity [4]. In continuous of our interest in the synthesis of indole derivatives [5], we have decided to study the synthesis of 1,3-thiazoles linked to indole moiety in the position 4' instead of the position 2' in the Camalexin.



Camalexin Thiabendazole

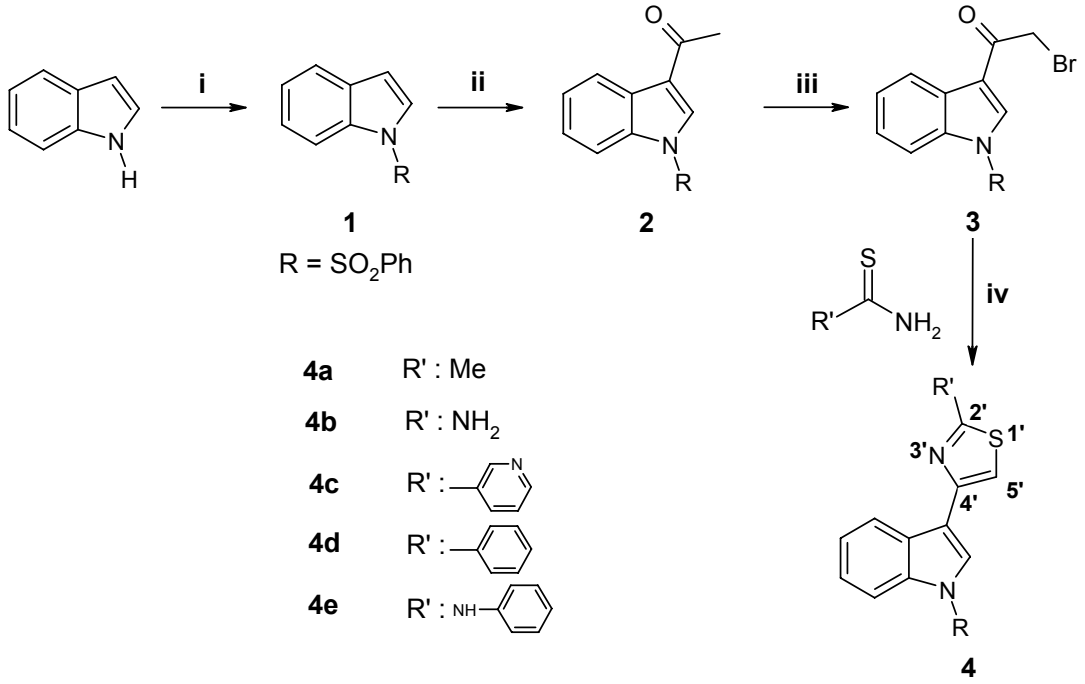
Figure 1. *Chemical structure of camalexin and thiabendazole*

In the literature there are described several methods for synthesis of Camalexin, based on the reaction of indolylmagnesium iodide with 2-bromothiazole [3], or heating of indole-3-carboxamide with P_2S_5 and chloroacetaldehyde diethylacetal in ethanol [6], or reductive cyclization of 2-formamidophenyl-2'-thiazolyl ketone upon heating with TiCl3 and zinc dust [7], or reaction of 1-sulfonyl-3-indole with active zinc and following Pd catalysed arylation with 2-iodothiazole [8]. Recently, the reaction of indol-3-carboxaldehyde with methyl L-cysteinate hydrochloride, followed by oxidation and decarboxylation, fournished Camalexin in 12% yield [9]. To achieved the synthesis of compound **4** (scheme 1), it was decided to use the condensation of 1-benzenesulfonylbromoacetylindole **3** with various thioureas.

RESULTS AND DISCUSSION

We originally attempted to prepare the target compound **4a** (scheme 1) from bromo-acetylindole **3** (R = H) and methylthiourea in refluxing ethanol. However, attempted condensation was unsuccessful and afforded decomposition product. In order to prevent this, we required as starting material a N-protected indole and the protecting group of choice was benzenesulfonyl group. To this end the N-benzenesulfonyl indole **1** (R = SO_2Ph) was prepared in 90% yield from the reaction of indole with benzenesulfonyl chloride, in anhydrous THF and in the presence of sodium hydride [10]. The C3-selective Friedel-Crafts acylation [11] of **1** fournished the 3-acyl product **2**, and selective bromination of the α-carbon of the carbonyl group with $CuBr_2$ gave the product **3** in good yield.

The condensation of bromoacylindole **3** with various thioureas carried out in ethanol at room temperature, provided the corresponding derivatives **4**. The benzenesulfonyl protecting group can be removed from protected indoles by sodium hydroxide in refluxing ethanol, to afford the Camalexin analogous.



Scheme 1.

i) *NaH, THF, $PhSO_2Cl$, 0°C;* ***ii)*** *$(CH_3CO)_2O$, $AlCl_3$, CH_2Cl_2, r. t.;* ***iii)*** *$CuBr_2$, $CH_3CO_2C_2H_5$, r. t.;* ***iv)*** *Thiourea, C_2H_5OH, r. t.*

CONCLUSION

In this contribution, we reported a series of new substituted thiazoles linked in position 3 to indole moiety. The condensation of bromoacetylindole with thioureas was employed as a key step for these syntheses.

EXPERIMENTAL

Melting points were determined on a Koffler block. The NMR spectra were recorded at 300 K DMSO-d_6 on a Bruker Avance DPX 250. The chemical shifts are expressed in parts per million relative to tetramethylsilane (TMS). The mass spectra were recorded on Perkin-Elmer SCIEX API 300 using ionspray methodology. Thin layer chromatography was performed on precoated plate of silica gel $60F_{254}$ (Merk) and the spots visualised using an ultraviolet lamp. Tetrahydrofuran (THF) was distilled under nitrogen from sodium benzophenone before use.

General procedure for the preparation of 4 :

To a solution of chloroacetylindole **3** (1equivalent) in absolute ethanol (20 mL), thiourea was added (1,2 equivalent), and the mixture was stirred at room temperature.

The precipitate formed was filtred and the solution concentrated in vacuum. Crystals precipitated out and were filtrered and washed with ethanol.

1-benzenesulfonyl-3-(2'-méthyl-thiazol-4'-yl) indole

yield : 96%, m. p. : 213 °C
^{1}H NMR (250 MHz, DMSO-d_6) δ 2,74 (s, 3H, CH_3), 7,33-7,45 (m, 2H, $H_{5'}$, H_{Ar}), 7,55-7,71 (m, 3H, H_{Ar}), 7,99-8,05 (m, 4H, H_{Ar}), 8,19 (d,1H, J = 7,5 Hz, H_{Ar}), 8,25 (s, 1H, H_2).
^{13}C : δ (ppm) 19,28 (CH_3), 113,88 (CH), 115,4 (CH), 117,9 (C), 122,24 (CH), 124,6(CH), 125 (CH),125,9 (CH), 127,4 (CH), 128,2 (C), 130,5 (2CH), 135,2 (C), 135,4 (CH), 137,3 (C), 146,8 (C),166,55 (C).

4-(1-benzenesulfonyl-1H-indole-3-yl)-thiazol-2-ylamine

yield : 82%, m. p. : 240 °C,
^{1}H NMR (250 MHz, DMSO-d_6) δ 7,31 (s, 1H, $H_{5'}$), 7,36-7,50 (m, 2H, H_{Ar}), 7,58-7,69 (m, 2H, H_{Ar}), 7,72-7,75 (m,1H, H_{Ar}), 7,90-8,05 (m, 4H, H_{Ar}), 8,34 (s, 1H, H_2) ;
^{13}C : δ (ppm) 103,8 (CH), 112,4 (C), 113,5 (CH),120,7 (CH), 124,4 (CH), 125,4 (C), 125,5 (CH), 125,9 (CH), 126,8 (C), 126,9 (2CH), 130 (2CH), 134,3 (C), 135,1 (CH), 136,5 (C), 169,4 (C).

1-benzenesulfonyl-3-(2-pyridin-3-yl-thiazol-4-yl)-1H-indole

yield : 71%, m. p. : 224 °C
^{1}H NMR (250 MHz, DMSO-d_6) δ 7,26 (s, 1H, $H_{5'}$), 7,33-7,57 (m, 7H, H_{Ar}), 7,94-7,97 (m, 2H, H_{Ar}), 8,05-8,16 (m, 3H, H_{Ar}), 8,35-8,40 (m, 1H, H_{Ar}), 8,69 (s, 1H, H_2) ;
^{13}C : δ 110,6 (C), 110,8 (CH), 111,9 (CH), 120,2 (CH), 121,7 (CH), 124,3 (CH), 124,7 (CH), 125,2 (CH), 125,5 (2CH), 127,7 (2CH), 128,6 (CH), 129,2(C), 133,5 (CH), 136,6 (C), 146,9 (CH), 148,1 (C), 150,8 (CH), 152,4 (C), 162,8 (C).

1-benzenesulfonyl-3-(2-phenyl-thiazol-4-yl)-1H-indole

yield : 81%, m. p. : 153 °C
^{1}H NMR (250 MHz, DMSO-d_6) δ 7,33-7,71 (m, 8H, $H_{5'}$, H_{Ar}), 8,02-7,07 (m, 5H, H_{Ar}), 8,25- (br s, 1H, H_{Ar}), 8,32-8,35 (m, 1H, H_{Ar}), 8,44 (s, 1H, H_2) ;
^{13}C : δ 113,3 (CH), 115,3 (CH), 117,5 (C), 121,9 (CH), 124,1 (CH), 124,7 (CH), 125,4 (CH), 126,2 (2CH), 126,8 (2CH), 127,8 (C), 129,3 (2CH), 129,9(2CH), 130,4 (CH), 132,8 (C), 134,6 (C), 134,8 (CH), 136,8 (C), 148,5 (C), 169,9 (C).

[4-(1-Benzenesulfonyl-1H-indole-3-yl)-thiazol-2-yl]-phenyl-amine

yield : 92%, m. p. : 189 °C
^{1}H NMR (250 MHz, DMSO-d_6) δ 6,98 (t, 1H, J = 7,5 Hz, H_{ar}), 7,31-7,45 (m, 5H, $H_{5'}$, H_{Ar}), 7,55-7,72 (m, 5H, H_{Ar}), 7, 99-8,16 (m, 4H, H_{Ar}), 8,20- (s, 1H, H_2), 10,44 (s l, 1H, NH) ;

^{13}C : δ 104,1 (CH), 113,4 (CH), 117,2 (2CH), 118,0 (C), 121,6 (CH), 124,0 (CH), 124,1 (CH), 125,3 (CH), 126,8 (2CH), 127,8 (C), 129,1 (2CH), 129,9 (2CH), 134,7 (CH), 134,8 (CH), 136,7 (C), 140,5 (C), 141,0 (C), 142,6 (C), 163,4 (C).

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