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LETTERS TO THE EDITOR

SIMPLE SYNTHESIS OF METHYL 1-(1,1-DIMETHYL-PROP-2-EN-1-YL)-1H-INDOLE-3-CARBOXYLATE

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Although few in number, indole derivatives containing a 1,1-dimethylpropen-2-yl (isopropenyl) fragment on the nitrogen atom are extremely interesting from the viewpoint of the medicinal chemistry of a class of naturally occurring compounds showing diverse biological properties. Some of these show anticancer, antifungal, antibiotic, anti-inflammatory, and antiviral activity [1-4].

The simplest member of the N-isopropenyl indole alkaloids is methyl 1-(1,1-dimethylprop-2-en-1-yl)-1H-indole-3-carboxylate (**1**) which is isolated from the *Aporpium caryae* basidiomycetes fungus and shows clear antifungal activity [4]. Compound **1** also serves as the synthetic precursor of other biologically active, naturally occurring indole derivatives i.e. methyl 1-(2,3-dihydroxy-1,1,-dimethylprop-2-en-1-yl)- and 1-(1,1-dimethyl-2,3-epoxyprop-2-en-1-yl)-1H-indole-3-carboxylates. Despite the relative structural simplicity of compound **1** its synthesis is not a trivial problem in view of the impossibility of directly introducing an isopropenyl substituent at position 1 of the indole. Up to this time the preparation of this compound involved two "indirect" synthetic strategies. The first of these consists of five stages (overall yield 60%) and is based on initial preparation of an N-isopropenylindoline, oxidation to the corresponding indole, and the introduction of a methoxycarbonyl group at position 3 in the final synthetic step [1, 2]. The second strategy consists of seven stages (overall yield 22%) and includes the preliminary transformation of an N-(1-ethoxycarbonyl)ethyl substituent in the N-indole to N-isopropenyl and then the introduction of the methoxycarbonyl substituent at position 3 [3].

We propose a novel, simple, and efficient method for the synthesis of compound **1** based on the use of the method reported recently by us to prepare N-substituted 1H-indole-3-carboxylic acids *via* a copper (I) iodide-catalyzed intramolecular Ullman reaction [5]. Refluxing equimolar solutions of methyl α-formyl-(*o*-bromophenyl)acetate (**2**) and the commercially available 1-methylbutyn-3-yl-2-amine in methanol gave the enamine **3** needed for cyclization and used in the following step without further purification. We have previously shown that cyclization of enamines prepared from α-branched primary aliphatic amines under standard conditions (CuI (5 mol %), K_3PO_4 (2 equiv.), 80ºC) occurs slowly, full conversion of starting enamine needing a prolonged reaction time (10-20 h) and the indole yield did not exceed 50% [5]. An analogous situation has been seen in the cyclization of enamine **3**, the yield of the N-isopropenyl indole **4** not exceeding 36% under these conditions. Increasing the reaction temperature to 140ºC caused only a minor increase in the yield to 50%.

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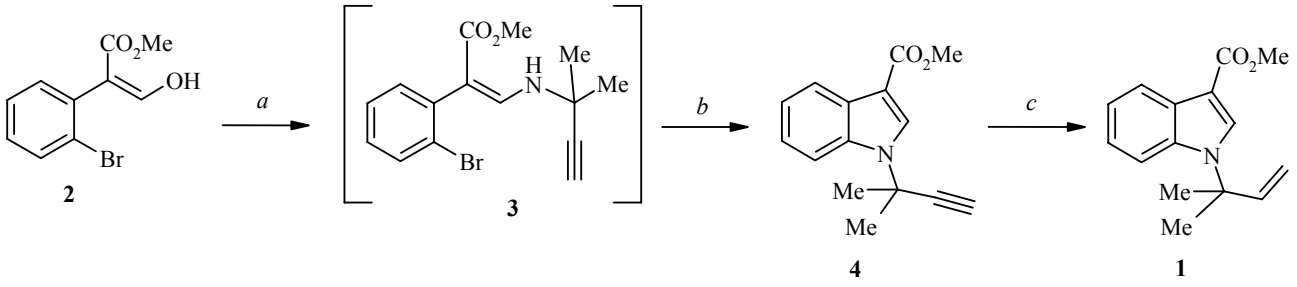
It should be noted that full conversion of enamine **3** was observed after 4 h and this is also evidently linked with the occurrence of side processes involving the terminal acetylene group. A marked increase in the yield of indole **4** can be achieved with the use of cesium carbonate as base with a simultaneous increase in the reaction temperature and shortened reaction time. In this case an almost quantitative conversion of the starting compound **3** is observed after 3 h and the indole is formed in 76% yield.

Subsequent partial hydrogenation of the N-propargyl indole **4** using a Lindlar catalyst gave the N-isopropenyl indole **1** in 96% yield.

Hence as a result of the route proposed by us the methyl 1-(1,1-dimethylpropen-2-yl-1)-1H-indole-3-carboxylate (**1**) could be prepared in three stages with an overall yield of 73%.



Reagents and Conditions. *a*. 1-Methylbutyn-3-yl-2-amine, MeOH, refluxing, 3 h; *b*. CuI (5 mol %), Cs_2CO_3 (2 equiv.), DMF, 140ºC, 3 h, overall yield of two stages 76%; *c*. H_2 (1.5 atm.), Lindlar catalyst (5 weight %), 25ºC, 3 h, 96%.

Methyl 1-(1,1-Dimethylprop-2-yn-1-yl) 1H-indole-3-carboxylate (4). 1-Methylbut-3-yn-2-yl-amine (0.161 g, 205 μl, 1.95 mmol) was added in one step to a solution of methyl α-formyl(*o*-bromophenyl)acetate (**2**), 0.5 g, 1.95 mmol) in methanol (15 ml), refluxed for 3 h, and the solvent was removed *in vacuo*. The residue was dissolved in DMF (8 ml) and cesium carbonate (1.271 g, 3.9 mmol) and copper (I) iodide (18.5 g, 0.1 mmol) were added to the solution. The flask was placed in an oil bath preheated to 140ºC and held at this temperature with vigorous stirring for 3 h. The reaction mixture was cooled, solvent was removed *in vacuo*, and the residue was dissolved in ethyl acetate (20 ml), washed with water (10 ml), HCl solution (2%, 10 ml), saturated aqueous $NaHCO_3$ solution, and dried over sodium sulphate. Solvent was removed and the residue was chromatographed on a silica gel column (0.040-0.063 mm) using hexane–ethyl acetate (20:1) to give the product (0.357 g, 76%) as a colorless, viscous liquid. ^{1}H NMR spectrum (Bruker Avance-400, $CDCl_3$, 400 MHz, residual deutero solvent as standard), δ, ppm (*J*, Hz): 2.01 (6H, s, $\underline{Me}_2C$); 2.67 (1H, s, C≡CH); 3.96 (3H, s, MeO); 7.31-7.37 (2H, m, H-5 and H-6); 7.92-7.98 (1H, m, H-7); 8.11 (1H, s, H-2); 8.26-8.31 (1H, m, H-4). ^{13}C NMR spectrum, (Bruker Avance-400, $CDCl_3$, 100 MHz), δ, ppm: 29.9 ($\underline{Me}_2C$), 51.0 (MeO), 73.5 (C≡$\underline{C}$H), 84.8 ($\underline{C}$≡CH), 106.8, 113.7, 121.9, 122.0, 122.4, 128.0, 131.2, 135.5, 165.6 (C=O). Mass spectrum (Finnigan MAT 90, direct introduction, 70 eV), *m/z* (I_{rel}, %): 241 $[M]^+$ (34), 175 $[M^+-H_2C=C(Me)C\equiv CH]$ (74), 144 $[M^+-H_2C=C(Me)C\equiv CH–OMe]$ (100), 109 (46). Found, %: C 74.71; H 6.29; N 5.77. $C_{15}H_{15}NO_2$. Calculated, %: C 74.67; H 6.27; N 5.81.

Methyl 1-(1,1-dimethylprop-2-en-1-yl)-1H-indole-3-carboxylate (1). Lindlar catalyst (5% $Pd/CaCO_3$, 3.5% Pb, Acros Organics) (17 mg) was added to a solution of compound **4** (0.357 g, 1.48 mmol) in methanol (20 ml) and the mixture obtained was vigorously stirred for 3 h at ~ 20ºC in a hydrogen atmosphere (initial pressure 1.2-1.5 atm.). The catalyst was filtered off, washed with additional methanol (20 ml), the solutions combined, and the solvent removed *in vacuo*. The residue was chromatographed on a silica gel column (0.040-0.063 mm) using hexane–ethylacetate (20:1) to give the product (0.345 g, 95%) as a colorless, viscous liquid darkened upon storage. The ^{1}H and ^{13}C NMR and mass spectra for compound **1** fully agree with those obtained earlier [4].

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