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A FACILE PREPARATION OF 2-ALKYLINDOLES - POTENTIAL INTERMEDIATES FOR ALKALOIDS

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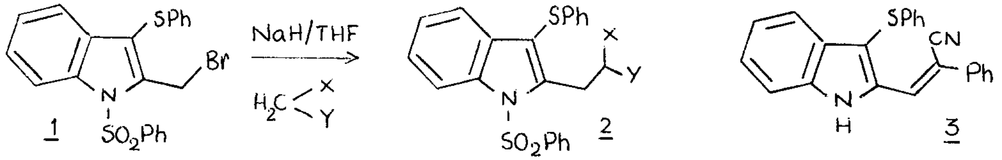
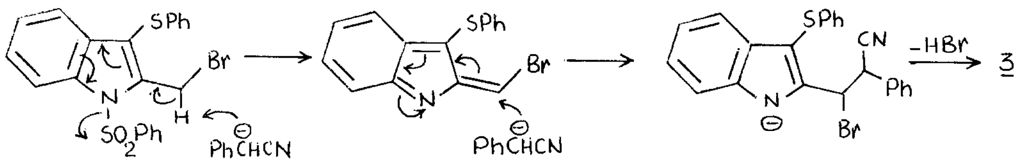
Abstract : The bromo compound 1 upon alkylation with active methylene compounds followed by the removal of PhS- and $PhSO_2$- groups furnished the title compounds.

Only a few methods are reported[1,2,3] for the synthesis of 2-substituted indoles, potential intermediates for a variety of medicinally important alkaloids. Recently we demonstrated[4] 1 as a potential synthon by synthesising isogramine and other 2-aminomethylindoles. Here we report the utility of 1 for the synthesis of 2-alkylindoles bearing functional groups in the side-chain which may serve as precursors for indole alkaloids. Alkylation of 1 with an equivalent of ethyl acetoacetate and diethyl malonate (NaH, THF,5-10°) afforded the corresponding monoalkylated products 2a(mp.102°) and 2b(mp.164°) respectively(80-90%). Under similar conditions alkylation of 1 with benzyl cyanide afforded the expected product 2c(mp.122°, 73%) along with the olefinic compound 3(mp.150°, 10%). Exclusive formation of 2c was observed at -24°.

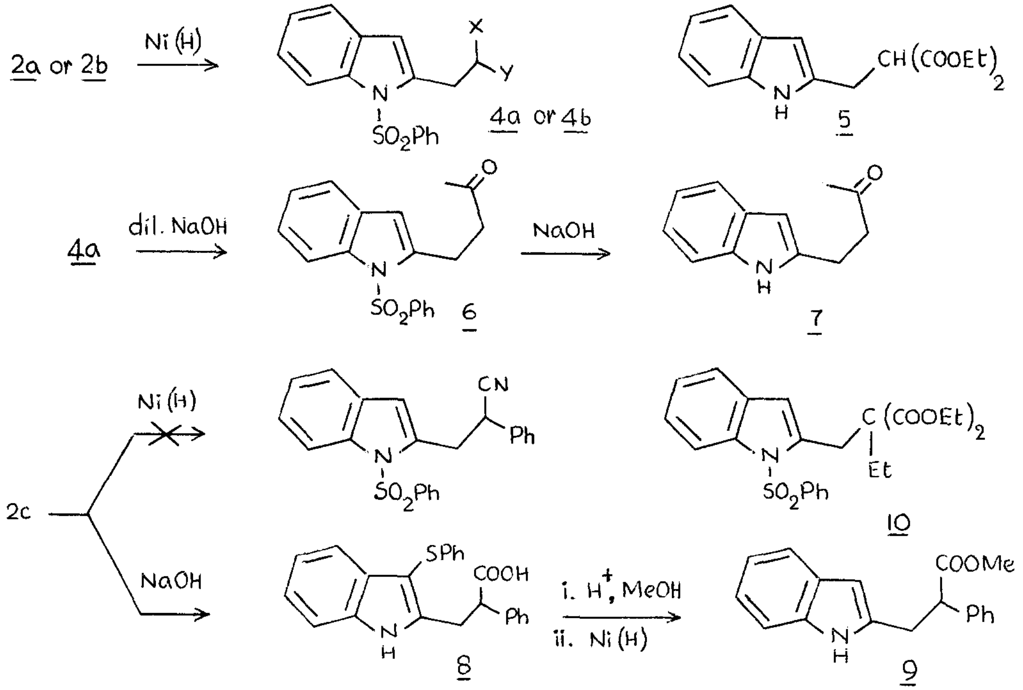


2a, X = $COCH_3$, Y = COOEt; 2b, X = Y = COOEt; 2c, X = Ph, Y = CN

Similar by-products were not obtained in the other cases. A plausible mechanism[2] for the formation of 3 is given below.



2a and 2b were desulfurised with Raney Nickel in boiling acetone(1h) to give 4a and 4b respectively(80-86%). Raney Nickel contaminated with a trace of alkali effected in the case of 2b both desulfurisation and desulfonylation in one step to give 5(mp.62°, 61%). Similar reaction did not take place for 2a. Ketonic hydrolysis of 4a with dilute alkali furnished 6(mp.140°, 77%). Hydrolysis of 4b and 6(10% NaOH-EtOH) yielded indole-2-propionic acid[5] and 7(mp.120°) respectively(60-70%). Attempted desulfurisation of 2c under various conditions was unsuccessful. Hydrolysis of 2c(10% NaOH-EtOH) furnished the acid 8(mp.180-182°, 73%) which was esterified(H^+,MeOH,89%, 118°) and desulfurised to give 9(mp.140°, 88%). All our attempts to alkylate 2b further were unsuccessful. However, second alkylation of 4b(NaH,THF,EtI) gave 10(65%).



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