IOSR Journal of Applied Chemistry (IOSR-JAC)
e-ISSN: 2278-5736.Volume 16, Issue 1 Ser. I (January 2023), PP 43-45
www.iosrjournals.org

Synthesis of 5-Heteroyl-4- Phenylthiazole

Dr. Jisha S P
Associate Professor of Chemistry, GFGC K R Puram

Date of Submission: 02-01-2023 Date of Acceptance: 15-01-2023

The thiazole ring can be constructed from acyclic precursors by a variety of approaches among which the classical Hantzsch [3 + 2] ring formation method remains the formost. Next to it stands in wide applicability, the [4 +1] ring construction route. For a practical synthesis of the thiazoles presently targeted, an appropriate route, among these suggested by previous work, need to be selected.

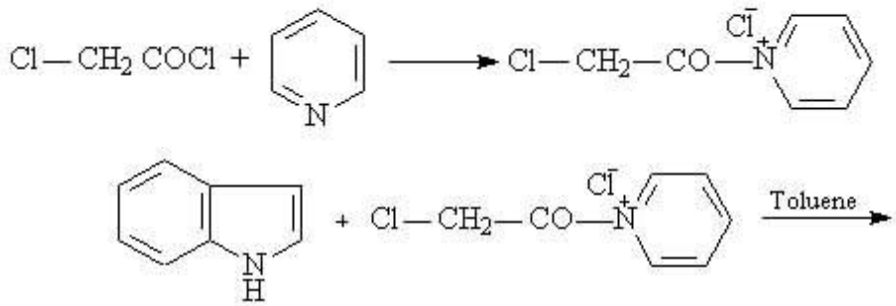
The use of an unsymmetrical 2-bromo-1,3-diketone derivative shown above would, result in the formation of isomeric thiazoles with 5-hetaroyl or 5-benzoyl substituents. In addition, such ketones, are not readily prepared. However, this can be done by the Claisen condensation of Me-CO-Het, where Het represents a heterocyclic group, with ethyl benzoate (or using acetophenone and the carbethoxyheterocycle) and once prepared, these have to be brominated. In contrast if a [4+1] approach is chosen, the acetyl heterocycle Me-CO-Het can be brominated and used in a[4+1] strategy. Further, the preparation of thioureas of the type RRN-CS-NH_2, is a struggle in itself even though their structure is deceptively simple.

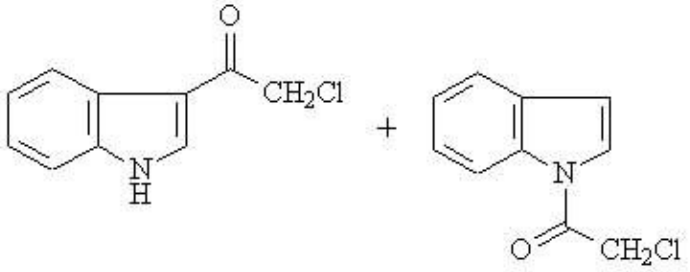
The [4+1] approach to thiazoles could also have two starting points; the benzoyl isothiocyanates or N-phenylbenzimidoyl isothiocyanate to provide the [C-N-C-S] thiourea synthon. The bromoacetyl heterocycle would be the, common, second componentthat would provide the C5 ring atom. Between these two, the benzoyl isothiocyanate can be prepared and used to access the required acylthiourea more easily. On this basis, we have adopted the route starting from benzoyl isothiocyanate leading to the acylthiourea synthon which could be reacted with bromoacetyl heterocycle and under specified conditions chosen not to lead to mixtures.

Objective:
The specific objectives of the work was to synthesise2-(N,N-dialkylamino)-5-(indol-3-oyl)-4-phenylthiazoles.

Preparation of 3-(2-chloroacetyl)indole

The reported method for the bromination of 3-acetylindole by copper bromide in chloroform and ethyl acetate did not perform well.. The synthesis of 3-chloroacetylindole has been reported by Bergman et al., by the Friedel-Crafts acylation of indole using chloroacetyl chloride in the presence of pyridine in dioxan or toluene. The chloroacetyl chloride was reported first to react with pyridine to form N-(α-chloroacyl)pyridinium salt which then reacted with indole to produce 3-(2-chloroacetyl)indole or 1-(2-chloroacetyl)indole.

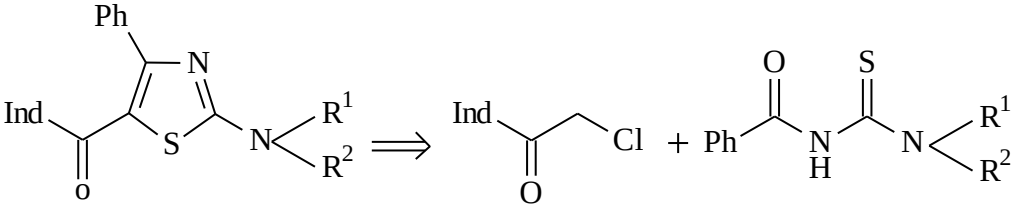




The study of Bergman and co-workers showed that the reaction is highly sensitive to temperature, catalyst and reactant catalyst ratio. When the temperature was at or below 30^0C 1-isomer was generally the predominant product. As the temperature was raised, the formation of 1-isomer decreased and that of the 3-isomer increased. At an optimum temperature of 55-60^0C, 80% of the 3-isomer (30) was formed along with some 1-isomer (31) as a side product, which could be removed by a column chromatography or recrystallisation. At high reaction temperatures (> 60^0C) the yield of the 3-(2-chloroacetyl)indole decreased, owing to the formation of 3-indolacyl pyridinium salt. Adopting the above method and modifying it to suit our laboratory condition in an attempt carried out with the collaboration of a co-worker in our laboratory, the required 3-(2-chloroacetyl)indole was obtained in 75% yield. The ^{1}H NMR spectrum of the chloroacetyl compound showed absorption peaks at δ 4.72 (2H,s, $COCH_2Cl$), 7.25 (2H,m), 7.49 (1H, m) and 8.24 (2H, m). This data was in agreement with reported values.

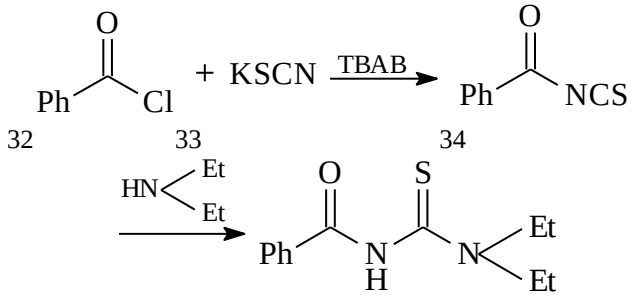
Synthesis of 2-(N,N-dialkylamino)-5-(indol-3-oyl)-4-phenylthiazoles

The retrosynthetic strategy adopted is shown below.

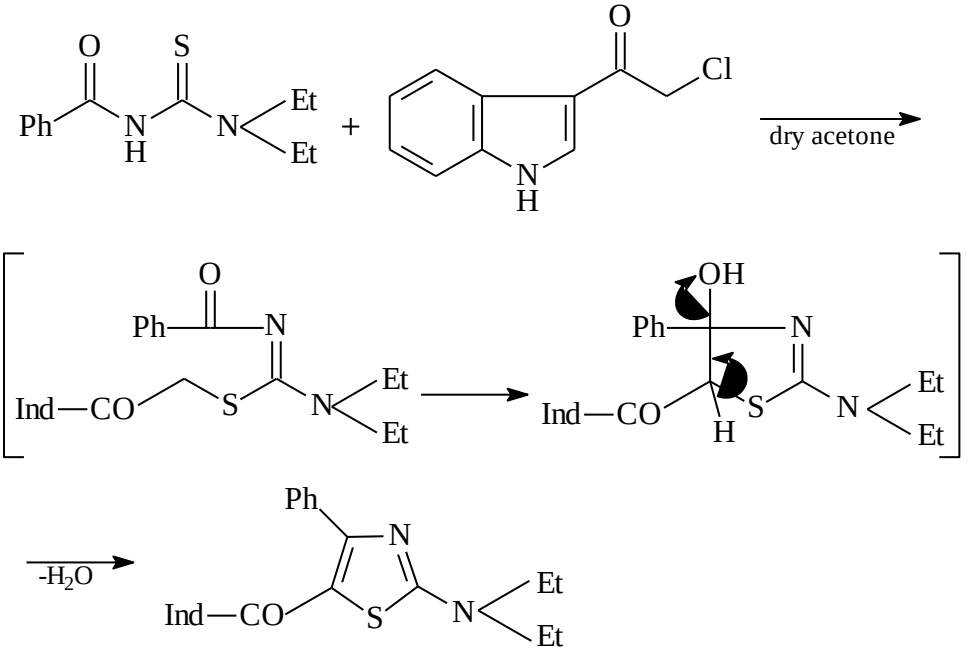


ind = indolyl

This approach required the preparation of N,N-dialkyl-N'-benzoylthiourea for the synthesis of 2-(N,N-dialkylamino)-5-(indol-3-oyl)-4-phenylthiazole. The synthesis can be exemplified by taking 2-(N,N-diethylamino)-5-(indol-3-oyl)-4-phenylthiazole as an example. The required N-benzoyl-N', N'-diethylthiourea was prepared by the reaction of benzoyl isothiocyanate (34) with diethylamine . The benzoyl isothiocyanate was prepared by using phase transfer catalyst and reacted with diethyamine in situ.



The reaction of N-benzoyl-N',N'-diethylthiourea with 3-(2-chloroacetyl)indole was carried out in dry acetone at reflux.



The workup and purification by crystallisation afforded a compound as brown crystals. The molecular composition of the compound was found to be $C_{22}H_{21}N_3OS$ by elemental analysis.

The IR spectrum showed bands due to νN-H and νC=O vibrations at 3184 and 1647 cm^{-1} respectively. The shift in C=O vibration at 1685 cm^{-1} in 3-acetylindole to 1647 cm^{-1} in the product indicated strong conjugation as well as a possibility of hydrogen bonding. The presence of a phenyl group was indicated by the strong bands at 757 and 684 cm^{-1} due to δ C-H of the phenyl ring. The benzenoid hydrogens of the indole ring showed the characteristic C-H out of plane deformation band at 770 cm^{-1} due to the fused 1,2-disubstituted benzene ring. The ^{1}H NMR spectrum (300 MHz, DMSO-d_6) of the compound showed a triplet of six hydrogens at δ 1.30. A quartet of four hydrogens at δ 3.58 was assigned to the two ethyl groups on the nitrogen attached to C2. The aromatic region showed an absorption with peak integral corresponding to five hydrogens as a multiplet at δ 7.08-7.24. This was assigned to the H5 and H6 of indole ring along with three hydrogens of the phenyl ring. A multiplet seen at δ 7.28-7.38 was assigned to H7 of the indole ring. The multiplet at δ 7.50-7.60 was assigned to the remaining two hydrogens of the phenyl group. The peak centred at δ 7.46 due to one hydrogen was assigned to H2 and the multiplet at δ 8.10-8.18 to H4 of the indole moiety. The indole NH appeared at δ 11.47 as a broad singlet.

References

[1]. Brackman. J.C, et.al., *Bull. Soc. Chem. Belg*, **1987**, 96,809.
[2]. J. Bergman, J.E. Backvall and J.O. Lindstrom, *Tetrahedron*, **1973**, 29, 971.
[3]. Christopher J. Mody, Jonathan RA Raffey, M.A. Stephens, *Anticancer Drugs*, **1997**, 8, 489.
[4]. D.H. Williams and I.Fleming, "*Spectroscopic Methods in Organic Chemistry",* Edn.5, Mc Graw-Hill, **1995**, p. 159.
[5]. C. X. Yang, H. H. Patel, Y. Y. Ku, R. Shah and D. Sawick, *Synth. Commun.* **1997,** 27, 2125.
[6]. I.T. Hogan and Sainsbury, *Tetrahedron*, **1984**, 40, 681

Dr. Jisha S P. "Synthesis of 5-Heteroyl-4- Phenylthiazole." *IOSR Journal of Applied Chemistry (IOSR-JAC)*, 16(1), (2023): pp 43-45.