Asian Journal of Chemistry; Vol. 29, No. 10 (2017), 2232-2234

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2017.20739

Magnesium Catalyzed Dephenylsulfonylation: Synthesis of 5-Ethyl-1*H*-indole

S. VENKAT RAO*, H. HAVALE SHRIKANT, B. SANJITH KUMAR and G. SIVA KRISHNA

Chemical Research & Development, SMS Pharmaceuticals Ltd, Research Center (A DSIR Approved), Gagillapur, Hyderabad-500 047, India

*Corresponding author: E-mail: venkat@smspharma.com; svr.org@gmail.com

Received: 23 April 2017; *Accepted*: 15 July 2017; *Published online*: 31 August 2017; AJC-18526

A novel magnesium metal catalyzed synthesis of 5-ethyl-1*H*-indole from 5-[2-(phenyl sulfonyl)ethyl]-1*H*-indole by dephenylsulfonylation mechanism providing an alternative and attractive approach to 5-ethyl-1*H*-indole with high yields. This approach is for both the protected and unprotected indoles.

Keywords: Synthesis, 5-Ethyl-1*H*-indole, Magnesium turnings, Dephenylsulfonylation, Methanol.

INTRODUCTION

Indole derivatives are most important lead compounds in drug development due to their wide range of pharmacological activity and more abundance in nature. There are more than 2000 indole derivatives were reported in various classes of heterocyclic groups. Most generally applicable synthetic process for indole moiety involves ring closure literature reported. Dephenyl sulfonation of non-aromatic side chains was reported with sodium amalgam in methanol. But the first time here in this research the authors presented a new method for dephenyl sulfonylation with magnesium turnings and synthesis of targeted molecule 5-ethyl-1*H*-indole from 5-[2-(phenyl sulfonyl)ethyl]-1*H*-indole with good yield and purity.

Generally substituted indoles prepared by Fischer indoles synthesis [1] or by electrophilic substitution on benzo portion or pyrole portion of indoles or by functional group inter conversion methodology [2]. 5-Alkyl substitution reactions very tuff, when 1st, 3rd position is free by Friedal-Craft alkylation or acylation. After revealing the available literature of 5th position alkyl substitution of indole [3], it is understood that the process for making simple 5-ethyl-1*H*-indole is nowhere reported, but its 1st, 3rd substituted 5-ethyl indoles has reported [4] (C_5-alkylation by protecting indoles as N-acetyl and the bromide of 1, 3 protected indoles replaced with triethyl borate in presence of palladium(II) acetate).

The introduction of acyl substituents onto the 5th position of protected indolines were reported by Ketcha and Gribble [5] by simple Friedel Craft acylation of N-protected indoles.

In the course of synthesizing impurities of eletriptan hydrobromide drug master file deficient. It is tried to procure 5-ethyl-1*H*-indole (**2**) as a precursor for synthesis of Impurity-E. Fortunately, nowhere it is readily available and then started thinking for its synthesis. We were surprised to discover such a beautiful and simple reaction to synthesize 5-ethyl-1*H*-indole (**2**).

The dephenylsulfonylation reactions rarely reported synthetic procedures, this kind of dephenylsulfonylation reactions earlier tried (Fig. 1) with sodium amalgam (Na-Hg) in methanol [6].

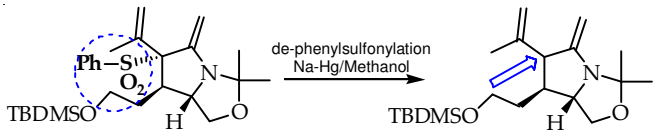


Fig. 1. Dephenylsulfonylation with sodium amalgam

The current invention relates the synthesis of 5-ethyl-1*H*-indole by dephenylsulfonylation of 5-[2-(phenyl sulfonyl)-ethyl]-1*H*-indole (**1**) with magnesium metal turnings in methanol. It is very interesting and novel approach to synthesis of 5-ethyl-1*H*-indole. 5-[2-(Phenyl sulfonyl)ethyl]-1*H*-indole (**1**) is commercially available and generally prepared by palladium catalyzed Heck-coupling reaction of 5-bromo-1*H*-indole with 1-(vinyl)-benzene.

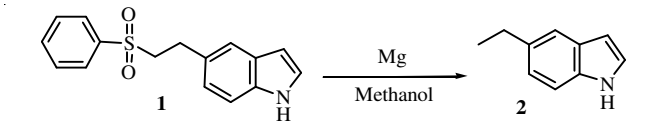
EXPERIMENTAL

The raw materials and reagents used for this research were purchased from Aldrich fine chemicals and Merck. The instrumentation like POLMON melting point apparatus used for melting points. TLC was performed on silica gel-G and spotting was done using iodine or UV light. The FT-IR spectra were recorded using Perkin-Elmer 100 instrument in KBr

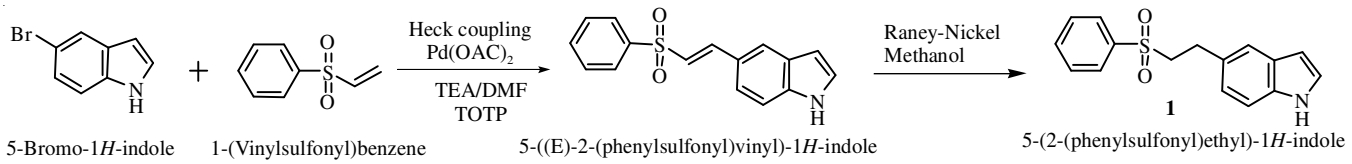
phase. ^{1}H, ^{13}C NMR spectra were recorded using a Varian 400 MHz instrument and Mass spectra on Agilent LC-MS instrument.

5-[2-(Phenyl sulfonyl)ethyl]-1*H*-indole (**1**) yield (98 %) was synthesized by Heck-coupling of 5-bromo-indole (10 g, 51 mol) with 1-(vinyl sulfinyl)benzene (6.25 g, 37.1 mol) in presence of palladium(II)acetate (0.17 g, 0.75 mol), tri-*ortho* toloylphosphine (TOTP) (2.5 g, 0.82 mol) and triethylamine (10 g, 9.88 mol) in DMF (105 mL) as solvent. The whole reaction mixture was heated to 100-115 °C for 3-4 h. The reaction mass cooled to 80-85 °C to done the hot filtration. The resulting filtrate mother liquor was quenched in 100 mL of water present in 500 mL in Erlenmeyer flask fitted with mechanical stirrer. The obtained aqueous layer transferred to 500 mL separating funnel and extracted with ethyl acetate (3 × 75 mL). The combined organics were washed with water (60 mL) and dried over anhydrous sodium sulphate (25 g). The obtained yellow colour solid compound of 5-[(*E*)-2-(phenyl sulfonyl)vinyl]-1*H*-indole (6.5 g, 22.9 mol) after concentration of the dried organic layer was directly taken for olefin reduction in Parr apparatus with (8 g, 9.3 mol, 50 % wet w/w) Raney-Nickel in methanol (100 mL). The catalytic hydrogenation performed under hydrogen pressure (H_2, 70-75 PSI) for 6-7 h under room temperature, after completion of the reaction by TLC analysis on silica gel with 40 % EtOAc-hexane). The excess Raney-nickel removed by passing through Celite 545 bed of Buchner flask (100 mL) filtration and concentrated the filtrate mother liquor under reduced pressure to afford the desired product 5-(2-(phenyl sulfonyl)ethyl)-1*H*-indole [7] (**1**) (**Scheme-I**) (5.57 g, yield 85.2 %) as off-white powder after isolating in MTBE solvent (15 mL) and it has the following spectral properties: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.91 (t, *J* = 2.7 Hz, 2H), 3.62 (t, *J* = 2.9 Hz, 2H), 6.30 (bs, 1H), 6.89 (d, *J* = 8.3 Hz, 1H), 7.31 (m, 1H), 7.65 (t, *J* = 7.7 Hz, 1H), 7.74 (t, *J* = 7.3 1H), 7.96 (d, *J* = 5.3Hz, 1H), 10.96 (s, 1H). ^{13}C NMR (100 MHz, CDCl3) δ: 28.34, 56.31, 100.67, 111.31, 119.35, 121.54, 125.52, 127.67, 127.76, 129.33, 133.68, 134.71, 139.01. FT-IR (neat, cm^{-1}): 3179, 2924, 2855, 2727, 1462, 1377, 721. Elemental analysis calculated for $C_{10}H_{11}N$: C, 82.72; H, 7.64; N, 9.65. MS calculated for $[M-H]^+$ 285.36, found 284.00. The purity was determined to be 99.2 % by HPLC chromatography.

Synthesis of 5-ethyl-1*H*-indole (2): A 250 mL clean and flame dried three necked round bottomed flask, the center neck was equipped with mechanical stirrer. The other two side necks of were fitted with 5 cm glass thermo-pocket and water condenser with nitrogen gas in-let tube to maintain inert atmosphere. The flask allowed to cool to room temperature, then added 5-[2-(phenyl sulfonyl)ethyl]-1*H*-indole (1) (15 g, 52.5 mmol, 1.00 equiv), anhydrous methanol (450 mL, 30 vol) and addition followed by magnesium turnings (15 g, 617 mmol, 11.75 equiv) under gentle stirring (about 290 rpm). It is observed that before addition of magnesium, the reaction mass is as light yellow in colour and then it is changed to pale yellow colour; once it is added with magnesium to the reaction mass. Slowly raise the temperature by heating (water bath) to 60-64 °C and maintain it for 3-4 h. While maintaining at reflux condition the whole reaction mass colour changed to ash in colour, then after maintaining to 8-9 h under the reflux condition a sudden frothing was observed in the reaction flask, it means the reaction gets initiated and this initiation indicates that the reaction is completed. After completion of the reaction the reaction mass was cooled to room temperature and filtered through a 100 mL Buchner funnel packed with Celite 545 bed (20 g) to remove the excess of magnesium turnings present in the reaction mass. The resulting filtrate mother liquor was distilled under reduced pressure at 40 °C. The resulting dark brown colour viscous liquid material taken in to water (200 mL), then it becomes clear aqueous solution. The resulting aqueous layer transferred to 500 mL separating funnel and extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine solution (50 mL saturated aqueous sodium chloride solution) and then dried over anhydrous sodium sulphate (10 g, 7.04 mol). The dried organic layer was distilled under reduced pressure (40 °C, 18 mm Hg) to afford the desired product 5-ethyl-1*H*-indole (7.10 g 98.50 %) as a light brown liquid (**Scheme-II**). The progress of the reaction followed by TLC analysis on silica gel with 30 % EtOAc-hexane as eluent and visualization with UV cabinet, the product (**2**) spot has at R_f = 0.80 (blue) and starting material (**1**) has R_f = 0.35 (blue) in the TLC plate. The chemical structure obtained product was confirmed by its spectral analysis of ^{1}H, ^{13}C NMR, FT-IR, mass. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.31 (t, *J* = 7.2 Hz, 3H), 2.75-2.80 (q, *J* = 7.2 Hz, 2H), 6.52 (m, 1H), 7.07 (d, *J* = 7.2 Hz, 1H), 7.17 (t, *J* = 7.2 Hz, 1H), 7.32 (d, *J* = 7.2 Hz, 1H), 7.49 (s, 1H), 8.04 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.45, 28.92, 102.14, 110.70, 119.02, 122.53, 124.20, 127.99, 134.18, 135.68. FT-IR (neat, cm^{-1}): 3179, 2924, 2855, 2727, 1462, 1377, 721. Elemental analysis calculated for $C_{10}H_{11}N$: C, 82.72; H, 7.64; N, 9.65. MS calculated for $[M+H]^+$ 145.09, found 146.2. The purity was determined to be 98.57 % by GC chromatography and as well as quantitative NMR calculation.



Scheme-II: Synthesis of 5-Ethyl-1*H*-indole from compound **1**



Scheme-I: Synthesis of 5-(2-(phenyl sulfonyl)ethyl)-1*H*-indole

Conclusion

The innovation presented in this research article; dephenylsulfonylation of the compounds having alkyl phenylsulfonyl groups with Magnesium (turnings) metal catalyst is successful. It is unique and novel approach of synthesis of 5-ethyl-1*H*-indole. It can be applicable to all the molecules, which were having alkyl phenylsulfonyl group as major functional group.

ACKNOWLEDGEMENTS

The authors are very thankful to Analytical Department for their constant support and also to the authorities of SMS Pharmaceuticals Ltd. for supporting to carry this research.

REFERENCES

1. R.J. Sundberg, The Chemistry of Indoles, Academic Press, New York p. 132 (1970).
2. J.H. Tidwell and S.L. Buchwald, *J. Am. Chem. Soc*., **116**, 11797 (1994); https://doi.org/10.1021/ja00105a021.
3. D.C. Beshore and C.J. Dinsmore, *Synth. Commun.*, **33**, 2423 (2003); https://doi.org/10.1081/SCC-120021830.
4. S.B. Madasu, N.A. Vekariya, M.N.V.D.H. Kiran, B. Gupta, A. Islam, P.S. Douglas and K.R. Babu, *Beilstein J. Org. Chem.*, **8**, 1400 (2012); https://doi.org/10.3762/bjoc.8.162.
5. D.M. Ketcha and G.W. Gribble, *J. Org. Chem.*, **50**, 5451 (1985); https://doi.org/10.1021/jo00350a001.
6. Y.C. Jung, C.H. Yoon, E. Turos, K.S. Yoo and K.W. Jung, *J. Org. Chem.*, **72**, 10114 (2007); https://doi.org/10.1021/jo701988j.
7. K. Laxminarayana, C. Rajendiran and K. Mukkanti, *Asian J. Chem.*, **25**, 1661 (2013); https://doi.org/10.14233/ajchem.2013.13702.