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Identification, Synthesis and Characterization of Principle Process Related Impurities in Isoproturon

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***Abstract* – Four process related impurities of Isoproturon were identified, synthesized and characterized. These structures were verified by synthesis of the impurities and comparison of the spectra and chromatographic (HPLC and TLC) retention data of the isolated and synthesized materials.**

***Keywords* – Isoproturon, *Ortho*-Isoproturon, *Meta*-Isoproturon, *Ortho*-Isoproturon Dimer *Meta*-Isoproturon Dimer And Characterization.**

I. INTRODUCTION

In the present era, there is a tremendous upsurge for the impurity profiling for the pharmaceuticals [1-3] and agrochemicals [4] products. As per regulatory guidelines for any products it is important to fix the limit for any specified and unspecified impurity in the product with their characterization, identification and quantification by analytical method. If we know the structure of impurity it is easy to avoid or minimize percentage of the impurity.

Isoproturon 3-(4-isopropyl phenyl)- 1,1-dimethyl urea is a herbicide, that is used in the control of annual grass and broad-leaved weeds in cereals.

The main purpose for this publication is to provide an ecofriendly reaction condition by avoiding phosgene gas gives two products in single step. This provides impurities required for HPLC method validation of isoproturon synthesis.

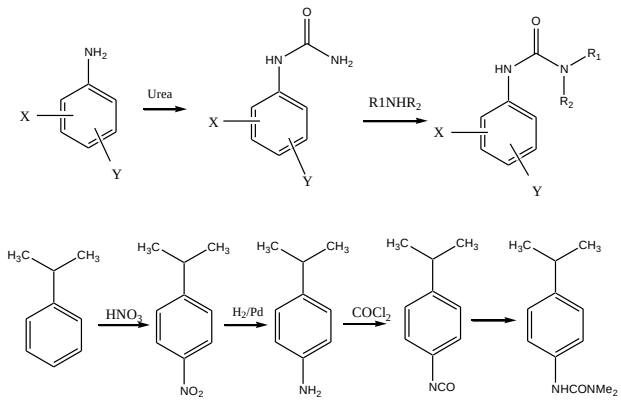

Fig.1. Isoproturon synthesis

Various methods available in literature for Isoproturon synthesis [5-7]. Isoproturon synthesis (Fig: 1) involves nitration of isopropyl benzene followed by nitro reduction to give 4-isopropyl aniline. 4-Isopropyl aniline further reacted with phosgene yields corresponding isocyanide derivative as a key intermediate, which on reaction with dimethyl amine gives final product dimethyl amine amide i.e. Isoproturon. This reaction sequence involves use of "phosgene" gas because of it's poisonous nature it is not convenient to use in laboratory.

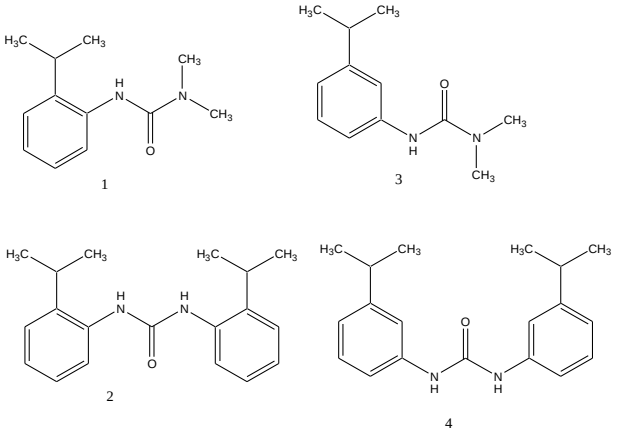

Fig.2. Isoproturon potential impurities

Various degradation pathway [8-9] of Isoproturon is also available in literature. There are four potential impurities (Fig: 2) known for Isoproturon product derives from *ortho* and *meta* derivatives of isopropyl benzene. Enrichment of above impurities present in small quantity by degradation of Isoproturon product was not possible so there was no option than to synthesize these impurities in pure form.

II. RESULTS AND DISCUSSION

Isoproturon isomer and dimer impurities were prepared by avoiding phosgene gas. Formation of both isomer and dimer impurities were found in one-pot reaction, dimer impurities were isolated simply by filtration.

III. EXPERIMENTAL

Thin-layer chromatography (TLC) were run on silica gel 60 F254 precoated plates (0.25 mm, Merck, Art. 5554) and spots were visualized inside an UV cabinet under short UV. Infrared spectra were recorded on Perkin Elmer Spectrum FT-IR Spectrometer by using ATR. ^{1}H-NMR spectra were recorded on Bruker 400 MHz with TMS as an internal standard. Mass spectra were obtained using a Agilent Series LC-MSD- TRAP-SL system. All other reagents and solvents were purchased from Aldrich (India) and S. D. Fine Chemicals, Mumbai. The solvents and reagents were used without purification.

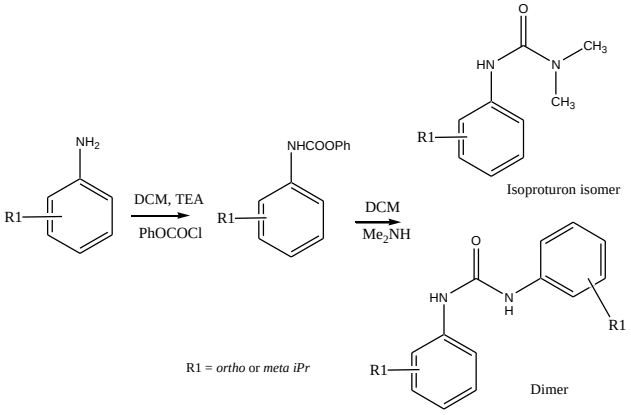

Fig.3. General Scheme for Isoproturon impurity synthesis

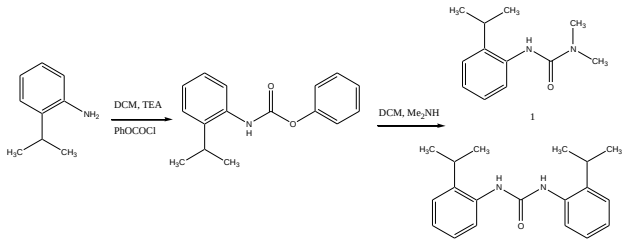

Fig.4. Reaction Scheme of ortho-isomer and (1) and Ortho-dimer (2)

IV. REPRESENTATIVE PROCEDURE

Preparation of 3-(2-isopropyl phenyl)- 1,1-dimethyl urea (1) and 1,3-bis-[2- (isopropyl phenyl) urea (2):

ortho-Isopropyl aniline (2.4 g, 0.015 mole) taken in methylene chloride 25 mL and triethyl amine (3.0 mL, 0.018 mole, 1.2 eq.). Reaction mixture was cooled at 0-5°C, phenyl chloroformate (2.5 mL, 0.016 mole, 1.1 eq.) diluted in methylene chloride 5 mL was added slowly to the reaction mixture by dropping funnel at 0-5°C. Reaction mixture then slowly warm to room temperature further stirred at same temperature for 3 hrs. Completion of reaction was monitored by TLC. After completion of reaction it was quenched with aq. NaOH (100 mL), water and then brine. Organic layer was separated and dried over sodium sulfate. In crude reaction mass 50 mL n-Hexane was added, solid obtained was filtered to get 1,3-bis-[2-(isopropyl phenyl) urea (**2**), *ortho*-dimer impurity. Filtrate was concentrated, crude product was pure enough and taken further for next stage.

Above crude product obtained from mother liquor was dissolved in methylene chloride 50 mL, cooled to 0-5 °C dimethyl amine gas (generated by heating dimethyl amine aqueous solution at 40-45°C) was purged for 30 mins., while stirring at 0-5°C. Reaction mixture was kept under closed container for overnight (~16 hr) under stirring at room temperature. Completion of reaction was monitored by TLC. After completion of reaction it was quenched with water (100 mL) and then brine. Organic layer was separated, dried over sodium sulfate and evaporated to get crude product. It was purified by silica column chromatography to give *ortho*- isoproturon isomer impurity 3-(2-isopropyl phenyl)-1,1-dimethyl urea (**1**) as off white solid compound. Yield: 12.27% (0.45 g, 95% pure), IR (cm^{-1}) 3223 (N-H), 2958-2866 (Aliphatic - H), 1627 (Amide N-H), 1504, 1456,1367 (Aliphatic - H bending), 1253 (C-O-C Asymmetric stretching), 761,748 (Ar- H bending), ^{1}H- NMR ($CDCl_3$, δ ppm): 7.55 (dd, 1H, Ar-H), 7.17 (d, 1H, Ar-H), 7.15-7.10 (m, 1H, Ar-H), 7.05-7.0 (m, 1H, Ar-H), 6.1 (s, 1H, N-H), 3.0 (s, 6H, NMe_2), 2.9 (m, 1H, -CH), 1.25 (d, 6H, iPr). MS: m/z 207 $[M+H]^+$, 229 [M+Na], 205 $[M-H]^-$. Melting point = 108.1°C.

Solid byproduct isolated by filtration from phenyl chloroformate reaction mixture was 1,3 bis-[2-(isopropyl phenyl) urea **(2)**, *ortho*-dimer impurity as off white solid compound. Yield: 14% (0.7 g, 85% pure), IR (cm^{-1}) 3305 (N-H), 2954-2866 (aliphatic-H), 1645 (amide N-H), 1585, 1537, 1440 (aliphatic -H bending), 1292-1236 (C-O-C asymmetric stretching), 758,750 (Ar- H bending), ^{1}H-NMR (DMSO-d_6, δ ppm): 8.29 (s, 2H, amide N-H), 7.6 (dd, 2H, Ar-H), 7.29 (dd, 2H, Ar-H), 7.15-6.9 (m, 4H, Ar-H), 3.25-3.15 (m, 2H, iPr), 1.20-1.18 (d, 12H, NMe_2). MS: m/z 297 $[M+H]^+$, 319 [M+Na], 295 $[M-H]^-$. Melting point = 231.3°C. *meta*-isomer and *meta*-dimer impurity were synthesized as per above procedure.

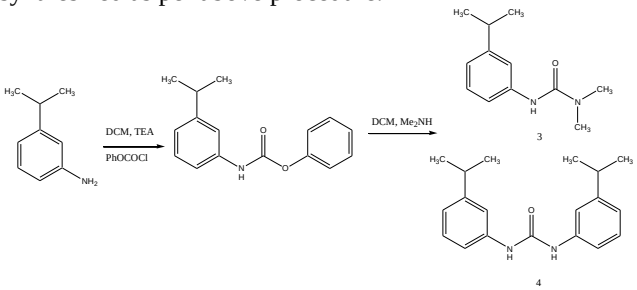

Fig.5. Reaction scheme for meta- isomer (3) and meta-dimer impurity (4)

Preparation of 3-(3-isopropyl phenyl) -1,1-dimethyl urea (3) and 1,3-bis- [3-(isopropyl phenyl) urea (4):

meta-Isopropyl aniline (3 g, 0.022 mole) taken in methylene chloride 30 mL and triethyl amine (3.72 mL, 0.026 mole, 1.2 eq.). Reaction mixture was cooled at 0-5°C, phenyl chloroformate (3.1 mL, 0.024 mole, 1.1 eq.) diluted in methylene chloride 5 mL was added slowly to the reaction mixture by dropping funnel at 0-5°C. Reaction mixture then slowly warm to room temperature further stirred at same temperature for 3 hrs. Completion of reaction was monitored by TLC. After completion of reaction it was quenched with aq. NaOH (100 mL), organic layer was washed with water and brine respectively. Organic layer was separated and dried over sodium sulfate. In crude reaction mass 50 mL n-Hexane was added, solid obtained was filtered, dried to get 1,3-bis-[3-(isopropyl phenyl) urea (4), *meta*-dimer impurity. Filtrate was concentrated crude product obtained was pure enough to be used for next stage.

Above crude product obtained from mother liquor was dissolved in methylene chloride 50mL, cooled to 0-5°C dimethyl amine gas (generated by heating dimethyl amine aqueous solution at 40-45°C) was purged for 30mins while stirring at 0-5°C. Reaction mixture was kept under closed container for overnight (~16 hrs) under stirring at room

temperature. Completion of reaction was monitored by TLC. Solid precipitated out was filtered out and filtrate was concentrated and crude product was purified by silica column chromatography to giving *meta*-isoproturon isomer impurity 3-(3-isopropyl phenyl)-1,1-dimethyl urea **(3)** as off white solid compound. Yield: 53% (1.5 g, 96% pure), IR (cm^{-1}) 3207 (N-H), 2958-2806 (aliphatic-H), 1643 (amide N-H), 1525, 1456,1367 (aliphatic-H bending), 1253 (C-O-C asymmetric stretching), 761,748 (Ar-H bending), ^{1}H- NMR ($CDCl_3$, δ ppm): 7.55 (dd, 1H, Ar-H), 7.17 (d, 1H, Ar-H), 7.15-7.10 (m, 1H, Ar-H), 7.05-7.0 (m, 1H, Ar-H), 6.1 (s, 1H, N-H), 3.0 (s, 6H, NMe_2), 2.9 (m, 1H, -CH), 1.25 (d, 6H, iPr). MS: m/z 207 $[M+H]^+$. Melting point = 98.4°C.

Solid byproduct isolated from phenyl chloroformate reaction mixture was 1,3-bis-[3- (isopropyl phenyl) urea (4), *meta*-dimer impurity as purple color solid compound having very high purity. Yield: 52% (2.1 g, 96% pure), IR (cm^{-1}) 3311 (N-H), 2954-2866 (aliphatic - H), 1645 (amide N-H), 1585, 1537, 1440 (aliphatic - H bending), 1292-1236 (C-O-C asymmetric stretching), 758,750 (Ar- H bending), ^{1}H- NMR (DMSO-d_6, δ ppm): 7.20 (m, 6H, Ar-H), 6.95 (d, 2H, Ar-H), 6.65 (bs, 2H, N-H), 2.85-2.75 (m, 2H, iPr), 1.16-1.14 (d, 12H, NMe_2). MS: m/z 295 $[M-H]^-$. Melting point = 164°C.

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