SCIREA Journal of Chemistry

http://www.scirea.org/journal/Chemistry

April 17, 2022

Volume 7, Issue 2, April 2022

https://doi.org/10.54647/chemistry15253

Synthesis of process related Dapsone impurities : Selective diazotization of aromatic di-amine

Mahesh Bandishti, Balaji Chaugule, Chinmoy Pramanik, Ganesh Karhade, Ashok Chaudhari *

API R&D Centre, Emcure Pharmaceuticals Ltd., ITBT Park, Phase-II, MIDC, Hinjewadi, Pune-411057, India

Fax: +91-20-35070081.

*E-mail: Ashok. Chaudhari @emcure.co.in

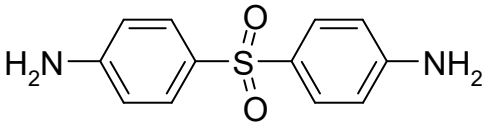
Abstract:

Process related two impurities of Dapsone were synthesized by applying cu-catalyzed conversions for the impurity profile and toxicological study. Controlled mono-diazotization of Dapsone followed by insitu iodination is the key step of our synthesis.

Keywords: Non-aqueous diazotization, Ullmann reactions, Process related impurities, Impurity Profile, Isoamyl nitrite and Hydroxylation.

Introduction:

Dapsone (**1**, **Figure 1**, 4, 4-diamino-diphenyl-sulphone (DDS)) is one of the most important and foremost drug for the treatment of leprosy and is also used in the treatment of malarial diseases and as an anti-inflammatory in acute ileitis.[1,2]



1

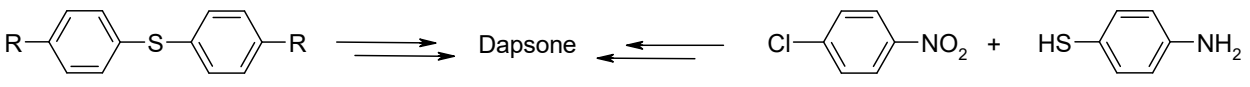
Figure 1 Dapsone

Dapsone in combination with Clofazimine prevents the inhibitory effect on neutrophil motility[3] and with Ethambutol and Rifampin it is used for the treatment of human eye disease.[4] Various methods were reported in literature for its synthesis and analysis (**Scheme 1**).[5]

Impurity profiling (i.e., identification as well as quantification of impurities) of an active pharmaceutical ingredient (API) is of fundamental significance for medical safety reasons and also for the drug effectiveness and is now receiving vital attention from regulatory authorities.[6] According to ICH (International Conference of Harmonization) guidelines, the level of total impurities must be reduced typically to less than 1.0 % and each individual impurity of 0.1 % or above must be identified in the active pharmaceutical ingredients (API).[7] Hence, considerable quantities of the impurity reference standards are required for both regulatory authorities and pharmaceutical companies, as each impurity needs to be quantified in the drug substances.

Results and Discussion:

During the commercial production of Dapsone, from the batch analysis data, two process related impurities, **4** and **5** were observed as a byproduct with ~ 0.3% along with the other reported impurities.[8](Figure-2)



R= NO_2, Cl, Br, NHAc

1

Scheme 1 : Synthetic routes for Dapsone

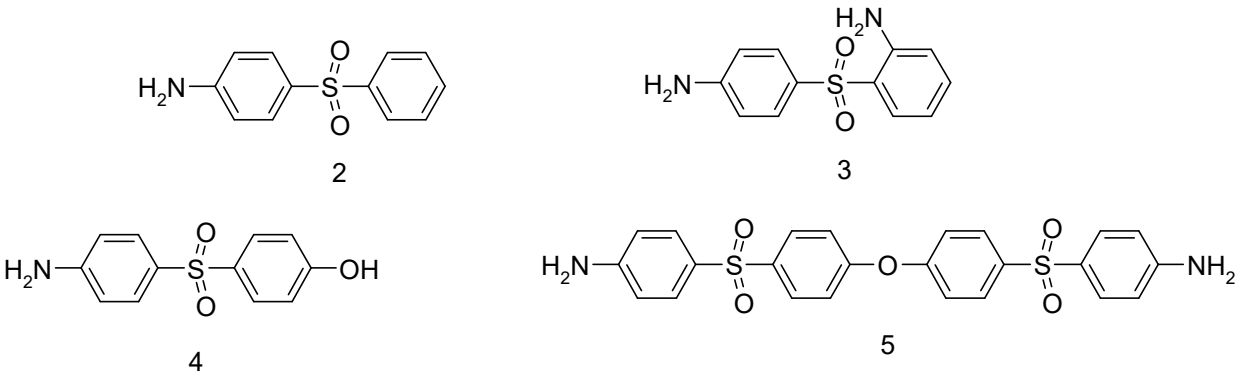
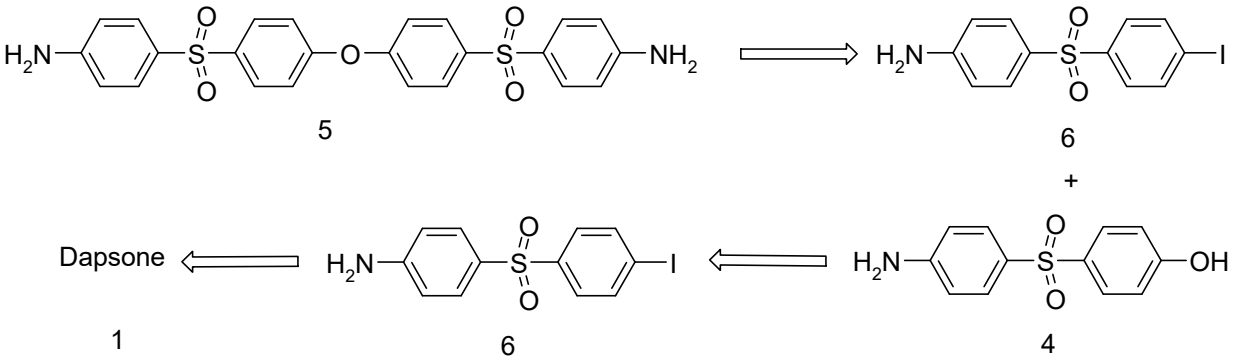
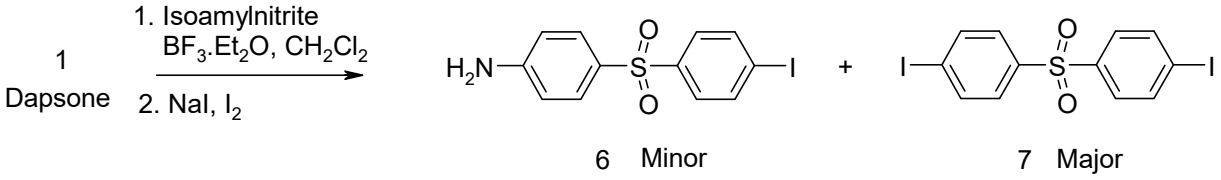


Figure 2 Process related impurities of Dapsone



Scheme 2 Reterosynthentic analysis



Scheme 3:

There are no reports in literature for the syntheses of these two impurities till date. Isolation from API for considerable quantities, are also very difficult due to very small quantity. So for our impurity profile and toxicological study, we deliberate to develop synthetic methods' for these two impurities in gram scale. Herein we wish to disclose our studies in developing routes to synthesis of these two impurities.

After the extensive literature survey, to avoid the multistep synthesis, and protection/de-protection strategy, we envisioned that shortest way to obtain the target impurity is desymmetrization of Dapsone i. e. controlled diazotization of one amino group of Dapsone and

concomitant functionalization. Accordingly, we intended to perform controlled diazotization of Dapsone followed by Sandmeyer,[9] to obtain the monoiodinated compound **6**, which on hydroxylation would result impurity **4**. Finally, etherification of compound **4** with itself or with halide **6** would provide us the required O-dimer impurity **5** (**Scheme 2**).

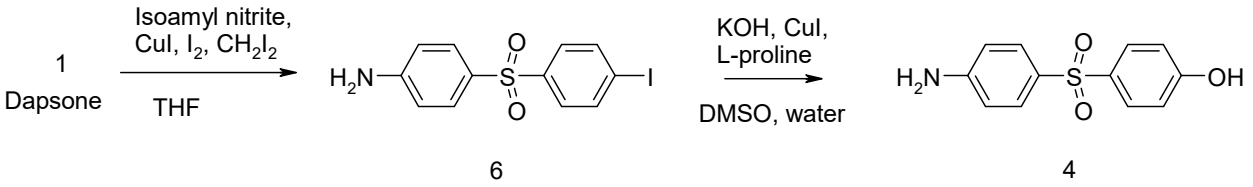
Since the discovery of Cu–mediated Ullmann reaction,[10] several Cu catalyzed methodologies[11] were reported till date, some of them are already proved their efficiency, during the complex natural product/pharmaceutically important molecules synthesis. During our embattled impurities synthesis, we contemplated Cu-metal catalyzed reactions might be very applicable for the various steps.

Controlled iodination via diazotization of one amino group of Dapsone following classical diazotization in aqueous medium is very difficult task. Doyle et. al[12] in a recent note described the use of tert-butyl nitrite and boron trifluoride etherate in methylene chloride or ether solutions to effect the conversion of aryl amines into their diazonium fluoroborate salts in high yields. More ever, recently, Zhu et al[13] reported controlled iodination of aromatic diamino derivative (2, 5 dibenzoyl 1, 1 diamino benzene) via diazotization using Doyle's protocol with 66% yield of the monoiodinated compound. Now, Dapsone (**1**) on diazotization following their technique, after isolation of the precipitated diazoniumfluoroborate salts, it was treated with sodium iodide (1.1 eq) and iodine (0.1 eq), to our surprise only 10% monoiodinated compound **6** was obtained along with diiodo derivative **7** as major product (**Scheme 3**).

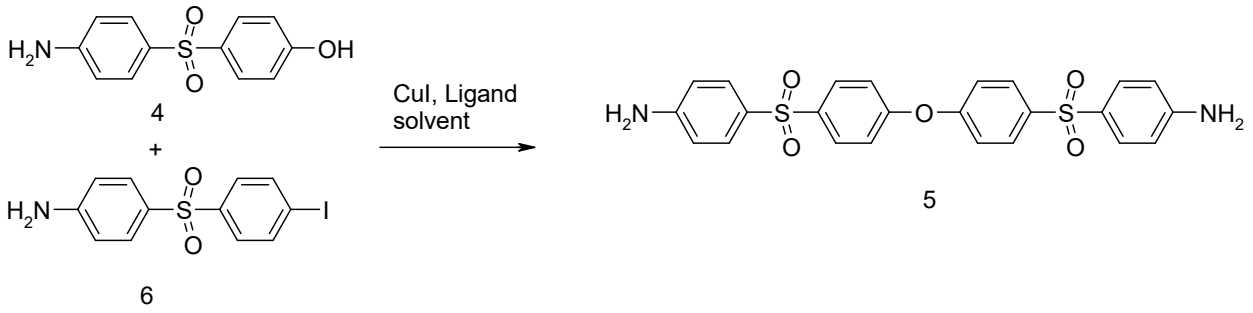
Further diazotization in non aqueous medium followed by insitu halogenations drawn considerable attention due to their easy work up, high yield of the desired product.[14] Consequently following Matsuda et al[14], Dapsone on treatment with isoamyl nitrite, CuI, iodine and diiodomethane in THF, monoiodinated compound **6** was obtained with 65% yield (**Scheme 4**).

For the hydroxylation of the aryl iodide, initially, we thought due to the strong electron withdrawing group at the *para*-position, heating with KOH may be helpful. Accordingly, we tried the hydroxylation of aryl iodide **6** with KOH in DMSO: water (1:1) mixture at 100 ^{o}C, after 15 h, 30% yield of the hydroxyl product was obtained with recovery of unreacted iodo compound **6**. Subsequently we screened variety of ligands such as TMEDA, DMEDA, L-Proline, TBAB and solvent systems like DMSO, water, DMSO/water or DMF/water under heating condition.[15] Better

results were obtained with L-proline as ligand (10 mol %) in DMSO: water (1:1) solvent in presence of CuI catalyst (10 mol %) and KOH as a base with 68% yield of phenol **4.**



Scheme 4:



Scheme 5:

The hydroxylation product **4** in hand, our spotlight was the synthesis of biaryl ether **5**. Biaryl ethers are typically made by the Ullmann reactions of phenol with aryl halides promoted by stoichiometric or greater quantities of copper at high temperature in polar solvents. Beside the recently developed various Pd catalyzed biaryl ethers building methodologies[16] and Cu catalyzed coupling of aryl boronic acids with aryl halide,[17] with catalytic amount of different copper salts and chelating ligand proved to be valuable catalyst precursors and Cesium carbonate is the typical base for these biaryl coupling (phenol with aryl halide) reactions.[17]

Recently Song's et al[17a] during their continuous efforts towards the development on simpler, mild biaryl ether formation methodologies, reported the use of TMHD as ligand in the CuI catalyzed biaryl ether formation using Cs_2CO_3 as base with very good yield. To our delight, the methodology worked well for our substrate with slight variation. We obtain 64% yield for impurity **5** (**Scheme 5**). Finally, the reaction condition was optimized by scrutinizing the effect of different bases, solvents and temperature.

In summary, we have accomplished short synthesis of process related two Dapsone impurities. The synthesis is based on desymmetrization by selective diazotization and insitu halogenetaion of dapsone. The synthetic procedure will be very useful for the organic chemists/pharmaceutical

industry to easy access of these two impurities for the impurity profile related study and regulatory requirement. Our strategy, desymmetrization/controlled functionalization of aromatic diamine, will also be useful for the synthesis of structurally related compounds

Experimental Section

Material and methods

The 1H NMR spectra of compounds were recorded on Varian 400 MHz instrument in DMSO-d_6. The deuterated solvents used for the recording of the NMR spectra were purchased from Merck. Mass analysis was carried out on AB sciex API 2000 model. All the chemicals used for the synthesis were commercial grade and used as it is without purification

Synthesis of 4: **4-((4-aminophenyl)sulfonyl)phenol**

To a solution of **6** (20.0 g, 0.055 mol) in DMSO (100 mL), were added L-proline (2.6 g, 0.022 mol), CuI (1.0 g, 0.0055 mol) and KOH solution (12.4 g KOH was dissolved in 100 mL water) under stirring and heated the reaction mixture to 90-100 ^oC for 12 h. After completion of the reaction (monitored by TLC), reaction mixture was cooled to 25-30 ^oC and filtered through celite bed and the residue was washed with DMSO. Filtrate was diluted with water (1.0 L) and acidified with dil-HCl to pH 4. The product was extracted with ethyl acetate (100 mL x 4). The combined organic layer was dried over anhydrous sodium sulfate, filtered, evaporated under reduced pressure at below 45 ^oC to obtain a crude residue. The crude product was purified by silica gel column chromatography using ethyl acetate and hexane (40:60) as eluent to yield impurity **4** (9.4 g, 68%) as yellow colored solid. ^1H NMR (DMSO-d_6, 400 MHz, δ ppm): 10.4(brs, 1H), 7.6 (d, 2H, *J* = 8.7Hz), 7.5 (d, 2H, *J* = 8.6 Hz), 6.9 (d, 2H, *J* = 8.7 Hz), 6.6 (d, 2H, *J* = 8.6 Hz), 6.1 (brs, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 161.1, 153.2, 133.3, 129.0, 128.9, 127.0. 115.8, 113.0. ESI-Mass: For $C_{12}H_{11}NO_3S$ (M+H)/z: 249.29, Found: (M+H)/z: 250.2, (M+Na)/z: 272.1.

Synthesis of 6: **4-((4-iodophenyl)sulfonyl)aniline**

To a cold solution of Dapsone (40 g, 0.161 mol) in THF (200 mL), were added isoamyl nitrite (40 mL), copper iodide (32.6 g, 0.171 mol), iodine (8.2 g, 0.032 mol) and diiodomethane (80 mL) and stirred at 25-30 ^oC for 3 h. After complete consumption of the starting material, monitored by TLC, reaction mixture was diluted with THF (600 mL) and filtered through celite bed. The

filtrate was distilled out under reduced pressure to obtain a crude residue and product was purified by using silica gel column chromatography using ethyl acetate and hexane (40:60) as eluent to yield **6** (37.6 g, 65%) as light brown solid. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 7.9 (d, 2H, *J* = 8.6 Hz), 7.6(d, 2H, *J* = 8.6 Hz), 7.5 (d, 2H, *J* = 8.6 Hz), 6.6 (d, 2H, *J* = 8.6 Hz), 6.2 (brs, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 153.8, 143.0, 138.4, 129.7, 128.3, 124.9, 113.2, 113.2, 100.8. ESI-Mass: For $C_{12}H_{10}INO_2S$ (M+H)/z: 359.19, Found: (M+H)/z: 359.7, (M+Na)/z: 381.6

Synthesis of 5: 4,4'-(oxybis(4,1-phenylenesulfonyl))dianiline

To a suspension of Comp. **4** (2.5 gm, 0.010 mole), Comp. **6** (4.7 gm, 0.013 mole), CuI (0.95gm, 0.005 mole), Cs_2CO_3 (4.8 gm, 0.015 mole) in acetonitrile, was added TMHD (0.294 gm 0.005 mole) in a sealed tube. Reaction mixture was heated at 120 °C for 6h. Reaction mixture was cooled to room temp, CuI (0.476 gm, 0.0025 moles) was added, and again Reaction mixture was heated at 120 °C for 6h. Reaction mixture was cooled to room temp and diluted with acetonitrile (100 ml) and stirred at rt for 30 minutes. Reaction mixture was then filtered through cellite bed. Filtrate was distilled out under vacuum and residue was dissolved in ethyl acetate (150 ml) and washed with 5% aq KOH (50 ml) solution to remove the unreacted **4**. Ethyl acetate layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure and purified by silica gel column chromatography using ethyl acetate and hexane (1:1) as eluent to yield **5** (3.1 g, 64%) as light brown solid. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 7.8 (d, 4H, *J* = 8.7 Hz), 7.5 (d, 4H, *J* = 8.7 Hz), 7.2 (d, 4H, *J* = 8.7 Hz), 6.6 (d, 4H, *J* = 8.7 Hz), 6.2 (brs, 4H). ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 158.8, 153.6, 138.8, 129.5, 129.3, 125.6, 119.6, 113.1. ESI-Mass: For $C_{24}H_{20}N_2O_5S_2$ (M+H)/z: 480.57, Found: (M+H)/z: 481.1, (M+Na)/z: 503.0.

Acknowledgment :

The authors wish to thank Mr. Samit Mehta, our management and ARD group of Emcure Pharmaceuticals Ltd. for their willing support and constant encouragements.

References:

[1] Oelschlaeger H, Modrack H, (1986) *Arch Der Pharm 319* (1), 10.

[2] Ritter C V, Grisham M B, Granger D N,(1989) *Gastroenterology* , *96,* 811.

[3] Rensburg C E, Van Gatner E M, Lmkamp F M, Anderson R,(1982) *Antimicrob, Agents Chemother* , *21*(5), 693.

[4] Johnson L A, Wirostko E, US Patent 4 220 657 (**1978**).

[5] a. Allegrini P, Napoletano C, Razzetti G, Castaldi G and US 0192929, **2008**.

b. Roblin R O, Williams J H,U S Patent No. 2227400, **1941**.

c. Weijlard J, Messelry J P, U S Patent No 2385899, **1945**.

d.Villa M, Faveri C D, Zanotti R, Ciardella F, Borin F, US 0293970, **2008**.

e. Nariman A E, Maha A H, Samia A T, Ghada A S,(2021) Acta *Chromatographica,*

f. Adrian L, Ulrike H, (2021) *Journal of Pharamaceutcal and Biomedical Analysis* ***,198.***

[6] a. Go¨ro¨g S (2006) *Trends in Analytical Chemistry*, (*25*) 8, 755-757.

b. Rao N R, Kiran S S M, Prasanthi N L, (2010), *Indian J Pharm Educ Res 44*(3), 301- 310.

[7] a) ICH Guidelines, Q3A (R2), (2006) *Impurities in New Drug Substances*.

b) ICH Guidelines, Q3B (R2), (2006) *Impurities in New Drug Products.*

c) ICH Guidelines Q3C (R5), (2011) *Guideline for residual solvents*.

[8] a. Gannett P M, Johnson E M, Grimes M A, Myers A L, Deavers R E, Tracy T S, (2003) *Journal of Labelled Compounds and radiopharmaceuticals*, *46*(2), 107–114.

b. Mannan C A, Krol G, Kho B T,(1977) *J Pharm Sci* , *66*(11), 1618–1623.

c. Cheung A P, Lim P,(1977)*J Pharm Sci* , *66*(12), 1723–1726.

d. Gordon G R, Ghoul D C, Peters J H, (1975) *J Pharm Sci* , *64*(7), 1205–1207.

[9] a. Sandmeyer T, (1884) *Ber Dtsch Chem Ges, 17* (3), 1633–1635.

b. Sandmeyer T,(1884) *Ber Dtsch Chem Ges, 17* (4), 2650–2653.

[10] a. Ullmann F, Bielecki J, (1901)*Ber Dtsch Chem Ges,34*, 2174.

b. Ullmann F,(1903) *Ber Dtsch Chem Ges, 36,* 2382.

c. Ullmann F, *Sponagel P, (1905)Ber Dtsch Chem Ges, 38,* 2211

[11] Evano G, Blanchard N, Toumi,(2008) M. *Chem Rev*, *108*, 3054-3131.

[12] Doyle M P, Bryker W J, (1979)*J Org Chem, 44*, 1572.

[13] Chang J, Liu R, Zhu H, (2009) *X-ray structure analysis*, *25*, 73.

[14] Matsuda A, Shinozaki M, Yamaguchi T, Homma H, Nomoto R, Miyasaka T, Watanabe Y, Abiru T,(1992) *J Med Chem 35*, 241-252.

[15] Zhao D, Wu N, Zhang S, Xi Su X, Lan J, You J,(2009) *Angew Chem Int Ed* , *48*, 8729-8732

[16] Chen G, Chan A S C, Kwong F Y ,(2007) *Tetrahedron letter,48*, 473-476.

[17] a. Buck E, Song Z J, Tschaen D, Dormer P G, Volante R P, Reider P J, (2002),*Org Lett 4*(9), 1623-1626,

b. Sawyer J S,(2000) *Tetrahedron* , *56*, 5045,

c. Theil F, *Angew Chem , (1999) Int Ed,* , *38*, 2345.

d. Lindley J. (1984) *Tetrahedron 40*, 1433.