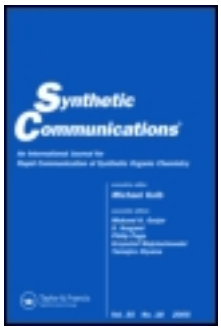

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A New Synthesis of β-Anilino-Chalcones by Regioselective Oxidation of β-Anilino-Dihydro-Chalcones using Iodine-DMSO

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Abstract

β-anilino-dihydro-chalcones readily undergo oxidation at α-to carbonylgroup region in presence of catalytic amount of iodine in dimethyl sulphoxide at 130 °C in high yield. Oxidation of allyloxy substituted β-anilino-dihydro-chalcones to β-anilino-chalcones is a preferred reaction over deallylation.

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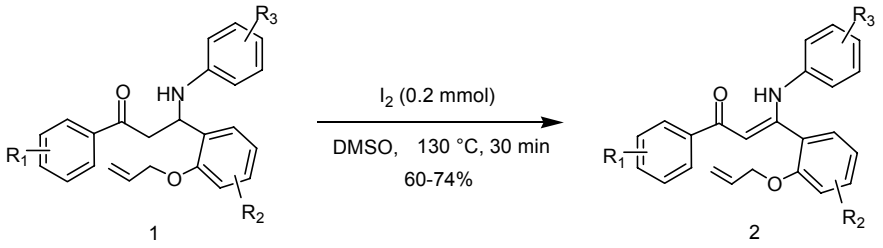

KEYWORDS: β-anilino-chalcone, dehydrogenation, iodine, dimethyl sulphoxide

INTRODUCTION

β-enaminones are important precursors of a wide variety of heterocycles[1] and pharmaceutical compounds.[2] They exhibits anti-epileptic,[3]molluscicidal, and larvicidal

activities[4] and employed as an intermediates for the synthesis of naturally occurring alkaloids.[5] β-Enamino ketones[6] were widely applied in the functional group transformation in the field of organic synthesis, including β-alkoxyvinyl ketones enamination,[7] 1,2-aryl migration,[8] 1,3-dicarbon enamination,[9]imidoyl chlorides with lithium enolates of alkyl propanoates to β-enaminones,[10] lithiateenamine acylation[11] and SonochemicalBlaise reaction.[12] These synthetic routes involve cyclic β–enaminones as well as β-anilinochalcones synthesized in the present work.

The most well-known and exploited route to β-enaminones involves the direct condensation of β-dicarbonyl compounds with amine at reflux in an aromatic solvent with azeotropic removal of water.[13] Several improved procedures have been reported including reaction of amines and 1,3-dicarbonyl compounds supported on silica with microwave irradiation,[14] clay montmorillonite K10/ultra-sound[15] or $NaAuCl_4$,[16] bismuth(III) trifluoroacetate,[9b] erbium triflate[17] or zirconium(IV) chloride,[18] cyclization of amino acids,[19] reductive cleavage of silylisoxazoles,[20] the direct condensation of primary amines and β-diketones in water.[21]These processes suffer from the limitations such as drastic reaction conditions, low yields tedious work-up procedures, co-occurrence of several side reactions and need of purification of adducts. Another route for the synthesis of β-enaminones is from chalcones and anilines. They react to give β-amino ketones[22] which can be converted to β-enaminones. But this method increases number of steps. That means to obtain β-enaminones oxidation of β-amino ketones is the only option.

K. C. Nicolaou et al. reported the dehydrogenation of aldehydes and ketones to α, β-unsaturated carbonyl compounds by using IBX.[23] Here, proper care is required in handling hazardous o-iodoxybenzoic acid. Although synthesis of β-enamino ketones was reported from endoglucal via hypervalent iodine,[24] dehydrogenation of chalcone by using iodine in dimethylsulphoxideis not reported yet. Thus, to report high yielding and simple method for the synthesis of β-enamino ketones is of immense importance.

RESULT AND DISCUSSION

β-Anilino-dihydro-chalcones were prepared as a starting material for the synthesis of β-anilino-chalcones by Mannich reaction. Ammonium chloride reagent has been used in various reactions. It effectively promotes multi component reactions for the synthesis of many heterocyclic compounds.[25]

Flavones were synthesized from 2'-allyloxy-chalcones by allyl deprotection procedures using iodine in dimethyl sulphoxide reagent.[26] In this reaction allyl group is first deprotected and 2'-allyloxy-chalcones then oxidatively cyclized to flavones. Allyloxy-β-anilino-dihydro-chalcones were subjected to the same reaction condition to get 4-amino-flavones. For the synthesis of 4-amino-flavone derivatives (**5i-p**)it is necessary to have allyloxy-β-anilino-dihydro-chalcones (**4i-p**). Hence we protected salicylaldehyde by allyl group and then subjected to Mannich reaction condition (Scheme 1). It was smoothly converted to allyloxy-β-anilino-dihydro-chalcones (**4i-p**). First time we reported the preparation ofMannich type bases by using allyloxy salicylaldehydes (**2**).

Earlier, deallylation study has been done for various substrates by using iodine in dimethylsulphoxide at 130°C.[26,27] Similarly same reagent was applied for catalytic dehydrogenation in nitrogen and oxygen containing heterocycles.[26,28,29] Allyloxy-β-anilino-dihydro-chalcones (**4i-p**) could be converted to 4-amino-flavones (**5i-p**) by using I_2-DMSO reagent[26] in one step. The reaction of allyloxy-β-anilino-dihydro-chalcones (**4i-p**) with (0.2 mmol) iodine in dimethyl sulphoxide at 130°C was completed in 30 minutes. In the ^{1}HNMR spectra of the product, the protons of allylic functionality (δ 4.63, 5.31, 6.01) remain intact but protons CH_2 (δ3.14) and CH (δ 5.27) was disappeared.A new proton was appeared in the aromatic region. In GCMS single product was observed and in MS, the mass of product was less by 2 than the substrate. This has confirmed the oxidation of a substrate at α-to carbonyl group region. That means allyloxy-β-anilino-dihydro-chalcones (**4i-p**) has been oxidized to allyloxy-β-anilino–chalcones (**6i-p**). It was observed that catalytic amount of iodine in dimethyl sulphoxide was unable for the deprotection of allyl group. Instead of deallylation, oxidation was observed. In earlier study it was observed that deallylation takes place by iodine in dimethylsulphoxide at 130°C however, in present work under the same reaction condition dehydrogenation of β-anilino-dihydro-chalcone is preferred over deallylation. For detail study, the reaction of allyloxy-β-anilino-dihydro-chalcone (**4i**) with iodine in dimethyl sulphoxide to give allyloxy-β-anilino- chalcone (**6i**) is selected as an appropriate model reaction. We optimized catalyst loading using different amount of catalyst (Table I).

Initially allyloxy-β-anilino-dihydro-chalcone (**4i**) was heated with 0.1 mmol iodine in dimethyl sulphoxide. There was no reaction below 130°C. Temperature of reaction

mixture was increased to 130°C. The product was formed in 30 minutes but starting also observed on TLC plate. Then reaction was performed with 0.2 mmol of iodine at 130°C. From TLC it was confirm that the reaction completes in 30 minutes.0.2 mmol of iodine was sufficient to give desired product (6i) in high yield. No significant improvement in the yield was observed on increasing the catalyst amount from 0.2 mmol to 1 mmol. On increasing the temperature up to 140°C, the substrate was decomposed. No change in the product was observed after using the catalyst in excess amount and increasing the time for 1-2 hours. After standardizing the reaction conditions, various substrates of β-anilino-dihydro-chalcones (**4a-p**) were allowed to react with iodine in dimethylsulphoxide to give β-anilino-chalcones (**6a-p**) (Scheme 2). The results are summarized in Table II. This reaction was not pursued further for the preparation of 4-amino-flavones (**5i-p**). The study of 4-amino flavone synthesis by changing the reaction condition is in progress.

The formation of allyloxy-substituted-β-anilino-chalcones (**Table II, entry 9-16**) may due to the interaction of anilino group with iodine. Such kind of oxidation was observed in the conversion of pyrazolines to pyrazoles[29] and oxidation of tetrahydroindazole to dihydro indazole.[30] Regioselectivity in dehydrogenation at α-to carbonyl group region (i.e. CH_2-CH) to CH=C instead of CH=NH to C=N was observed. The proposed mechanism of oxidation is given in the Scheme 3.

CONCLUSION

We have successfully synthesized allyloxy-β-anilino-dihydro-chalcones of three components such as acetophenones, allyloxy salicylaldehydes and anilines in presence of

ammonium chloride in methanol. A simple and efficient method was presented for oxidation of β-anilino-dihydro-chalcones to β-anilino-chalcones using I_2-DMSO reagent. However, regioselective oxidation of allyloxy substituted β-anilino-dihydro-chalcones at α-to carbonyl group regionis a preferred reaction over deallylation.

EXPERIMENTAL

TLC was performed on E-Merck precoated 60 F_{254} plates and the spots were rendered visible by exposing to UV light and iodine. Melting points were determined with an Electro thermal model 9100 apparatus and are uncorrected. IR spectra were recorded on a Shimadzu 8000 spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded on Varian spectrometer. Chemical shifts (δ) are reported in ppm and with reference to tetramethyl silane as internal standard. Mass spectra (GCMS) were recorded on a Shimadzu Q 5050 spectrometer.

General Procedure For The Oxidation Of B-Anilino-Dihydro-Chalcones To B-Anilino-Chalcones By Using I_2-DMSO Reagent

To a solution of β-anilino-dihydro-chalcones (1 mmol) in DMSO (5 ml) was added iodine (50.8 mg, 0.2 mmol) and the reaction mixture was heated in an oil bath at 130°C for 30 min. After cooling, iodine was removed by washing with a saturated solution of sodium thiosulphate and water. The product was then extracted with ethyl acetate and dried over Na_2SO_4 and solvent was evaporated. The product (**6a-p**) was purified by column chromatography (hexane/ethyl acetate, 9:1).

Spectral Data Ofselected Compounds

3-(2-Allyloxyphenyl)-1-(4-Chlorophenyl)-3-(Phenylamino) Propen-1-One (6j)

IR (KBr): 3383, 3030, 1674, 1525 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=8.00-7.97 (m, 1H, aromatic-H), 7.96-7.82 (m, 2H, aromatic-H), 7.56-7.41 (m, 5H, aromatic-H), 7.38-7.33 (m, 1H, aromatic-H), 7.27 (m, 1H, C-H), 7.15-6.96 (m, 4H, aromatic-H), 6.12-6.01 (m, 1H, CH), 5.31 (dd, J = 17.4, 10.5 Hz, 2H, CH_2), 4.63 (d, J = 1.5 Hz, 2H, CH_2); ^{13}C NMR (300 MHz, $CDCl_3$): δ=189.99, 69.15, 40.72; MS(*m*/*z*): 389 (M+ ion); Anal. calcd for $C_{24}H_{20}ClNO_2$: C, 73.94; H, 5.17%. Found: C, 73.79; H, 5.27%.

3-(2-Allyloxyphenyl)-1-Phenyl-3-(3-Chlorophenylamino) Propen-1-One (6k)

IR (KBr): 3365, 2924, 1683, 1599 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=8.05-7.96 (m, 2H, aromatic-H), 7.83 (d, J = 7.8, 1H, aromatic-H), 7.56-7.42 (m, 5H, aromatic-H), 7.36-7.30 (m, 2H, aromatic-H), 7.26-7.19 (m, 1H, C-H), 7.06-6.96 (m, 3H, aromatic-H), 6.14-6.02 (m, 1H), 5.32 (dd, J = 17.4, 10.5 Hz, 2H, CH_2), 4.66 (d, J = 5.4 Hz, 2H, CH_2); ^{13}C NMR (300 MHz, $CDCl_3$): δ=189.74, 69.10, 40.64; MS(*m*/*z*): 389 (M+ ion); Anal. calcd for $C_{24}H_{20}ClNO_2$: C, 73.94; H, 5.17%. Found: C, 73.68; H, 5.32%.

Complete experimental and spectral details are available online the Supplementary Information.

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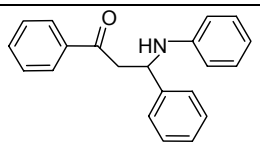
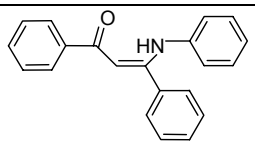
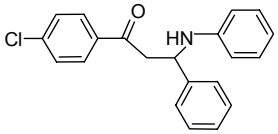
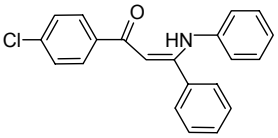
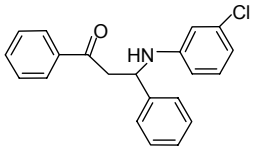
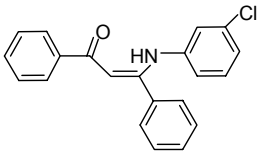
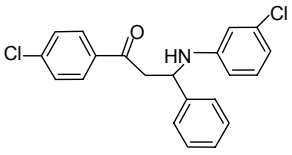
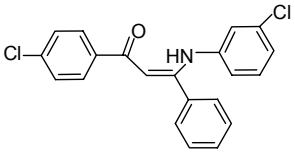
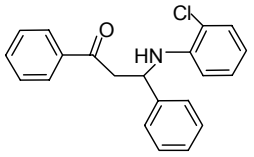
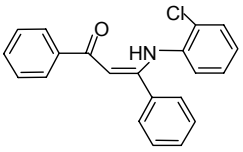
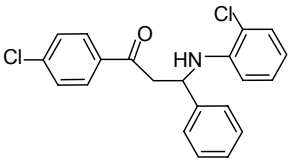
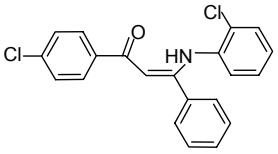
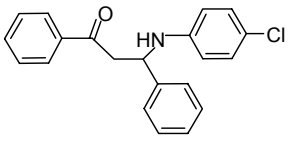
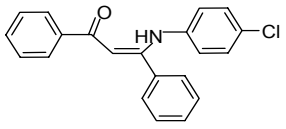
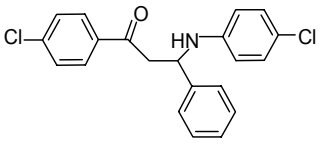
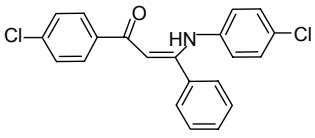
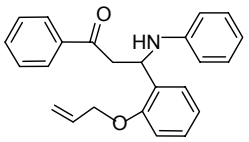
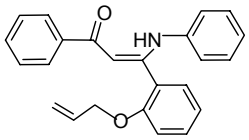
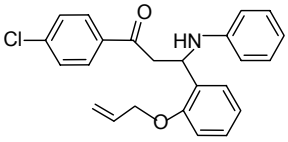
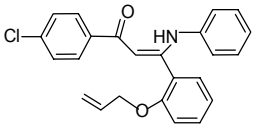
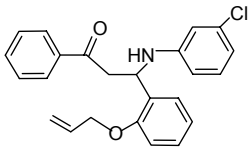
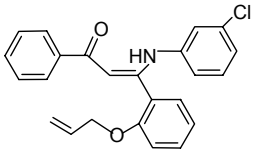
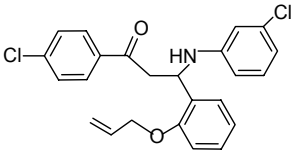
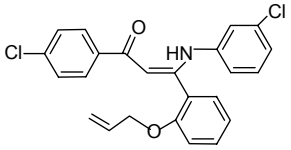
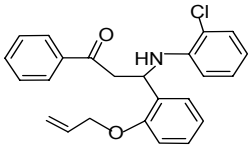
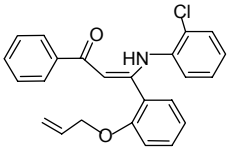
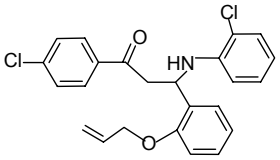
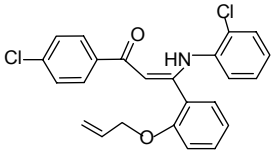
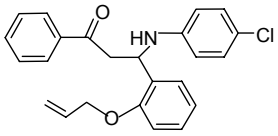
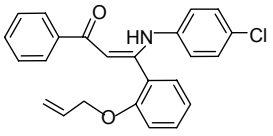
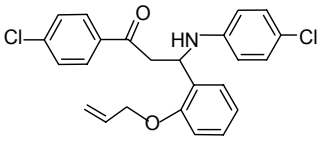
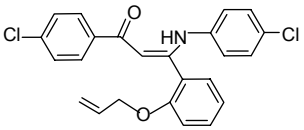
Table I Temperature Effect andQuantity of iodine

Entry	Compound	Iodine (mmol)	Temperature (°C)	Time (h)	Yield (%)[a,b]
1	4i	0.1	Below 130	0.5	0
2	4i	0.1	130	0.5	35
3	4i	0.2	130	0.5	67
4	4i	0.5	130	0.5	68
5	4i	1.0	130	0.5	68

[a]Isolated yields of the product [b]Products are characterized by spectral analysis

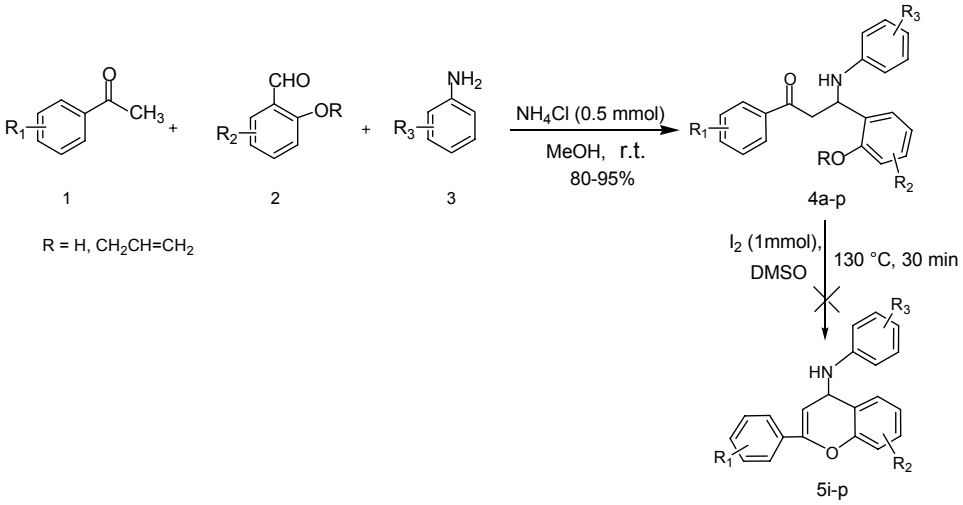
Table II Oxidation of β-anilino-dihydro-chalcones by using I_2-DMSO reagent.

Entry	4	Starting (4)	6	Product (6)	Yield (%)[a,b]
1	4a		6a		65
2	4b		6b		67
3	4c		6c		74
4	4d		6d		70
5	4e		6e		64
6	4f		6f		63
7	4g		6g		61
8	4h		6h		60

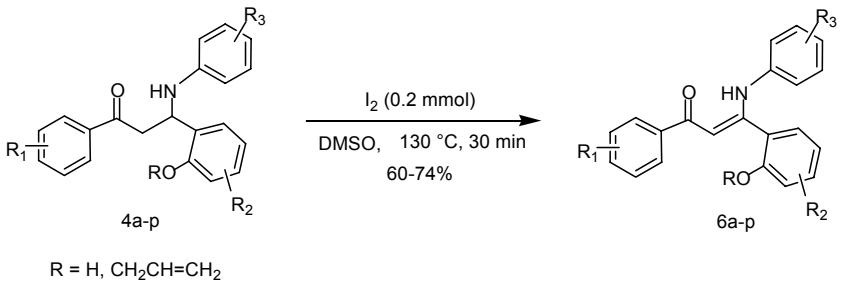
9	4i		6i		67
10	4j		6j		68
11	4k		6k		73
12	4l		6l		71
13	4m		6m		68
14	4n		6n		62
15	4o		6o		70
16	4p		6p		67

[a]Isolated yields of the product [b]Products are characterized by spectral analysis

Scheme 1 Synthesis of β-anilino-dihydro-chalcones



Scheme 2 Oxidation of β-anilino-dihydro-chalcones by using I_2-DMSO reagent.



R = H, $CH_2CH=CH_2$

Scheme 3 Plausible mechanism of oxidation of β-anilino-dihydro-chalcones by using I_2-DMSO reagent.