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Green Approach Toward the Synthesis of N-Substituted Anilines via Smile Rearrangement Using Amberlite IR-400 Resin

H. Sudhakar[1], G. Pavana Kumari[2], R. Venkata Nadh[3], Naveen Mulakayala[4]*

[1]Department of Polymer Science and Technology, Sri Krishnadevaraya University, Anantapur - 515 003, Andhra Pradesh, India. [2]Department of Chemistry, Sri Satya Sai Institute of Higher Learning, Anantapur - 515 001, Andhra Pradesh, India. [3]Department of Biotechnology, Vignan University, Vadlamudi, Guntur - 522 213, Andhra Pradesh, India. [4]Clearsynth Labs Ltd., Research Centre, Plot No. 177, IDA-Mallapur, Hyderabad - 500 076, Andhra Pradesh, India.

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ABSTRACT

A new method for the synthesis of N-alkyl anilines from phenols using silica sulfuric acid as a catalyst is described via smiles rearrangement. The synthesized anilines are handy intermediates in the organic synthesis.

Key words: *N-alkylaryl amines, Smiles rearrangement, Silica sulfuric acid, N-alkyl amines.*

1. INTRODUCTION

C-N bonded compounds are very familiar in organic synthesis and also in bioactive agents. It is highly focused area of research in organic synthesis [1]. The Buchwald and Hartwig transition metal catalyzed C-N bond forming reaction has become one of the major reactions in the medicinal chemistry laboratories [2]. Recently, C-N bond formation using Pd or Ni catalyzed coupling of phenolic derivatives are aryl sulfonates [3], ethers [4], esters [5], sulfamates [6] and carbamates [5,7] were well-documented.

Smiles rearrangement is one of the established method for converting phenols to anilines [8,9].

This method is useful for the preparation of iomeprol, [9a] dibenzo [b, f] pyrazole [1,5-d] [1,4] oxazepines [9b], dibenzoxazepinones [9c], benzo [1,4] oxazin-3(4H)-ones [9f], pyrido [1,4] thiazinone derivatives [9g] and carbazole based alkaloids such as mukonine, calusenine and murrayafoline A [9h] (Figure 1).

With an interest in the solid resin and reusable catalyst, we are interested to test the smile rearrangement using amberlite IR-400 resin catalyst [10].

1.1. General

Unless stated otherwise, reactions were performed under nitrogen atmosphere using oven-dried glassware. Reactions were monitored by thin layer chromatography on silica gel plates (60 F254), visualizing with ultraviolet light or iodine spray. Flash chromatography was performed on silica gel (230-400 mesh) using distilled hexane, ethyl acetate, dichloromethane. ^{1}H NMR and ^{13}C NMR spectra were determined in $CDCl_3$ or DMSO-d_6 solution using 400 MHz spectrometers, respectively. Proton chemical shifts (δ) are relative to experimental tetramethylsilane (TMS, δ = 0.00) as an internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet), as well as b (broad). Coupling constants (J) are given in hertz. Melting points were determined using melting point apparatus and were uncorrected. MS spectra were obtained on a mass spectrometer.

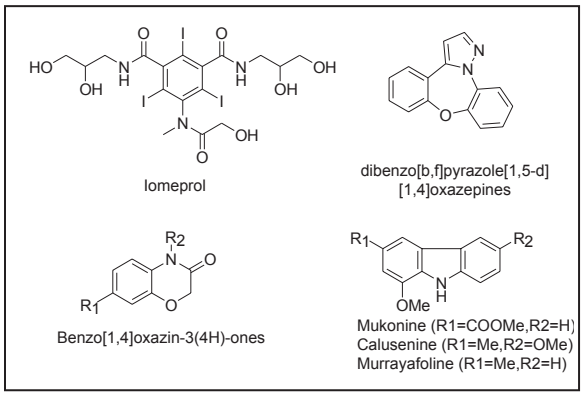


Figure 1: Synthetic routes structures of iomeprol, dibenzo [b,f] pyrazole [1,5-d] [1,4] oxazepines, benzo [1,4] oxazin-3 (4H)-ones and carbazole alkaloids.

*Corresponding Author:
E-mail: naveen071280@gmail.com

1.2. Typical Procedure for the Synthesis of Chloro-acetamide

T-butyl amine (10.0 g, 0.136 moles) was added to a stirred solution of amberlite IR-400 basic resin (30 mol%) in DCM (100 mL), and the mixture was cooled to 5=10°C. $ClCH_2COCl$ (19.0 g, 0.168 moles) was added for 1 h. The mixture was warmed to RT and stirred for 2 h. The compound was extracted with MTBE (20 mL × 2), then washed with brine solution (20 mL), dried over anhydrous sodium sulfate (10 g), and then the concentrated. The product was isolated by filtration and washed with pet ether (20 mL) to give 2-chloro-N-t-butyl acetamide as a white solid.

The same procedure was repeated for the synthesis of 2-chloro-N-cyclohexyl-acetamide.

1.2.1. 2-Chloro-N-t-Butyl Acetamide (2)

White solid, mp 83-85°C (lit. mp 80-84°C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.41 (br s, 1H), 3.98 (s, 2H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 52.1, 43.8, 29.4. Mass: (m/z) 150.4 [M+1].

1.2.2. 2-Chloro-N-Cyclohexyl-Acetamide (3)

White solid; mp 106.5-108.3°C (lit. mp 105-106°C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.46 (s, 1H), 4.03 (s, 2H), 3.82-3.77 (m, 1H), 1.93-1.89 (m, 2H), 1.75-1.63 (m, 3H), 1.42-1.34 (m, 2H), 1.25-1.20 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 48.8, 42.9, 32.9, 25.5, 24.8. Mass: (m/z) 176.1 [M+1].

1.3. Typical Procedure for the Synthesis of Amide

Phenol (0.9 g, 0.0069 moles) and 2-chloro-N-t-butyl acetamide (2; 0.8 g, 0.0053 moles) were dissolved in toluene (20 mL) at RT. To this amberlite IR-400 resin (20 mole%) was added and heated to 105-110°C for 7 h. After completion of the reaction the reaction was filtered and the solvent was evaporated. The residue was stirred with 10% aq NaOH (20 mL) for 2 h at RT and the precipitate was filtered and washed with H_2O (20 mL) to give amide 3.

1.4. Typical Procedure for the Synthesis of Amine

Amide 3 (1 g, 0.00414 moles) was added to a stirred solution of amberlite IR-400 resin (20 mole%) and NMP (5 mL) in toluene (20 mL) at RT. The mixture was heated to 120-130°C for 12 h then cooled to 40-45°C. H_2O (20 mL) was added with stirring. The layers were separated, and the aqueous layer was extracted with toluene (10 mL). The organic layers were combined, washed with H_2O (2 × 20 mL), and concentrated to give amine 4.

1.5. Tert-Butyl-(4-Chloro-Phenyl)-Amine (4a)

Yellow liquid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15-7.13 (dd, *J* = 1.58, 1.41 Hz, 2H), 6.71-6.69 (dd, *J* = 1.52, 1.56 Hz, 2H), 3.42 (br s, 1H), 1.35 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.6, 129.7, 123.1, 119.5, 52.6, 30.1. Mass: (m/z) 184.2 [M+1].

1.6. Tert-Butyl-Naphthalen-2-yl-Amine (4b)

White solid; mp 48-49°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73-7.70 (d, *J* = 8.09 Hz, 1H), 7.69-7.67 (d, *J* = 8.58 Hz, 2H), 7.39-7.35 (t, *J* = 7.46 Hz, 1H), 7.25-7.22 (t, *J* = 7.41 Hz, 1H), 7.07-7.05 (d, *J* = 1.69 Hz, 1H), 6.94-6.91 (dd, *J* = 2.06, 2.06 Hz, 1H), 3.72 (br s, 1H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.3, 135.8, 129.5, 128.8, 128.4, 127.0, 127.0, 123.1, 121.8, 109.8, 52.4, 28.8. Mass: (m/z) 200.3 [M+1].

1.7. Biphenyl-4-yl-Tert-Butyl-Amine (4c)

White solid; mp 65-67°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59-7.57 (d, *J* = 7.54 Hz, 2H), 7.45-7.42 (t, *J* = 8.04 Hz, 4H), 7.32-7.29 (d, *J* = 7.86 Hz, 1H), 6.85-6.83 (d, *J* = 8.25 Hz, 2H), 3.62 (br s, 1H), 1.35 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): d 147.2, 142.1, 131.6, 129.5, 128.5, 127.2, 127.0, 118.0, 52.3, 30.9. Mass: (m/z) 227.2 [M+1].

1.9. Tert-Butyl-p-Tolyl-Amine (4d)

Colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02-6.99 (d, *J* = 8.10 Hz, 2H), 6.75-6.72 (d, *J* = 8.33 Hz, 2H), 3.22 (br s, 1H), 2.28 (s, 3H), 1.28 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.1, 129.9, 129.4, 119.9, 52.6, 30.8, 20.8. Mass: (m/z) 165.1 [M+1].

1.9. Tert-Butyl-Phenyl-Amine (4e)

Colourless liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19-7.15 (t, *J* = 7.77 Hz, 2H), 6.78-6.75 (m, 3H), 3.45 (br s, 1H), 1.35 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.7, 129.8, 119.2, 118.4, 52.3, 31.0. Mass: (m/z) 151.3 [M+1].

1.10. Tert-Butyl-(3-Chloro-Phenyl)-Amine (4f)

Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08-7.03 (t, *J* = 7.99 Hz, 1H), 6.74-6.69 (m, 2H), 6.59-6.57 (dd, *J* = 1.74, 1.44 Hz, 1H), 3.63 (s, 1H), 1.33 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.0, 135.4, 129.9, 117.6, 115.9, 114.8, 51.7, 29.9. Mass: (m/z) 184.4 [M+1].

1.11. Tert-Butyl-(3-Methoxy-Phenyl)-Amine (4g)

Colourless liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09-7.05(t, *J* = 8.34 Hz, 1H), 6.36-6.32 (m, 3H), 3.77 (s, 3H), 3.48 (br s, 1H), 1.33 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.2, 148.6, 129.7, 109.9, 103.8, 103.8, 55.9, 52.3, 29.9. Mass: (m/z) 180.5 [M+1].

1.12. (4-Chloro-Phenyl)-Cyclohexyl-Amine (7a)

White solid; mp 48.1-50.8°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09-7.06 (dd, *J* = 3.12, 3.04 Hz, 2H), 6.55-6.50 (dd, *J* = 8.72, 1.72 Hz, 2H), 3.55 (br s, 1H), 3.22-3.18 (m, 1H), 2.06-2.03 (m, 2H), 1.79-1.74 (m, 3H), 1.39-1.36 (m, 2H), 1.28-1.14 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): d 146.8, 129.9, 122.1, 115.0, 52.7, 34.2, 26.7, 25.8. Mass: (m/z) 210.4 [M+1].

1.13. Cyclohexyl-Naphthalen-2-yl-Amine (7b)

White solid; mp 77.7-78.9°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68-7.60 (m, 3H), 7.39-7.35 (t, *J* = 7.52 Hz, 1H), 7.22-7.18 (t, *J* = 7.41 Hz, 1H), 6.89-6.86 (dd, *J* = 2.12, 2.11 Hz, 1H), 6.83 (s, 1H), 3.72 (br s, 1H), 3.42-3.39 (m, 1H), 2.17-2.13 (m, 2H), 1.84-1.69 (m, 3H), 1.47-1.41 (m, 2H), 1.29-1.21 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.9, 136.2, 129.8, 128.5, 128.1, 127.1, 126.6, 122.6, 119.1, 105.6, 52.6, 34.2, 26.9, 25.9. Mass: (m/z) 226.3 [M+1].

1.14. Biphenyl-4-yl-Cyclohexyl-Amine (7c)

White solid; mp 79-82°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57-7.55 (d, *J* = 7.66 Hz, 2H), 7.45-7.39 (m, 4H), 7.27 (t, *J* = 3.26 Hz, 1H), 6.69-6.67 (d, *J* = 8.09 Hz, 2H), 3.65 (br s, 1H), 3.35-3.29 (m, 1H), 2.13-2.09 (m, 2H), 1.80-1.66 (m, 3H), 1.43-1.38 (m, 2H), 1.29-1.17 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.7, 142.2, 129.8, 128.8, 128.8, 126.7, 126.4, 113.7, 52.6, 34.3, 26.8, 25.9. Mass: (m/z) 252.4 [M+1].

1.15. Cyclohexyl-p-Tolyl-Amine (7d)

White solid; mp 46-48°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99-6.97 (d, *J* = 8.0 Hz, 2H), 6.55-6.53 (d, *J* = 8.16 Hz, 2H), 3.38 (br s, 1H), 3.26-3.24 (m, 1H), 2.25 (s, 3H), 2.07-2.03 (m, 2H), 1.79-1.64 (m, 3H), 1.39-1.35 (m, 2H), 1.31-1.15 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.0, 129.8, 126.9, 114.3, 52.9, 34.4, 26.9, 25.9, 21.2. Mass: (m/z) 190.4 [M+1].

1.16. Cyclohexyl-Phenyl-Amine (7e)

Colourless liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19-7.15 (t, *J* = 7.23 Hz, 2H), 6.69-6.65 (t, *J* = 7.16 Hz, 1H), 6.63-6.59 (d, *J* = 7.89 Hz, 2H), 3.54 (br s, 1H), 3.29-3.24 (m, 1H), 2.09-2.06 (m, 2H), 1.79-1.65 (m, 3H), 1.39-1.34 (m, 2H), 1.26-1.18 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.8, 129.5, 117.7, 113.6, 51.7, 33.5, 26.8, 25.9. Mass: (m/z) 176.1 [M+1].

1.17. (3-Chloro-Phenyl)-Cyclohexylamine (7f)

Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09-7.05 (t, *J* = 8.0 Hz, 1H), 6.60-6.58 (d, *J* = 7.96 Hz, 1H), 6.55-6.55 (d, *J* = 1.72 Hz, 1H), 6.47-6.44 (dd, *J* = 1.76, 1.8 Hz, 1H), 3.65 (br s, 1H), 3.26-3.20 (m, 1H), 2.15-2.12 (m, 2H), 1.79-1.66 (m, 3H), 1.42-1.15 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.4, 135.9, 131.0, 117.4, 113.3, 112.3, 52.4, 33.9, 26.7, 26.8. Mass: (m/z) 210.4 [M+1].

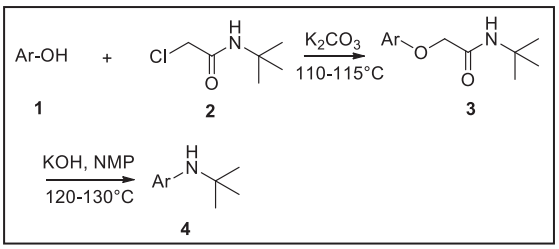
1.18. Cyclohexyl-(3-Methoxy-Phenyl) Amine (7g)

Colourless liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08-7.04 (t, *J* = 8.06 Hz, 1H), 6.26-6.20 (t, *J* = 8.34 Hz, 2H), 6.18 (s, 1H), 3.79 (s, 3H), 3.56 (s, 1H), 3.27-3.22 (m, 1H), 2.09-2.06 (m, 2H), 1.79-1.65 (m, 3H), 1.39-1.33 (m, 2H), 1.25-1.14 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): d 161.7, 149.6, 129.8, 107.2, 102.6, 99.6, 55.9, 52.6, 34.3, 26.8, 25.9. Mass: (m/z) 206.6 [M+1].

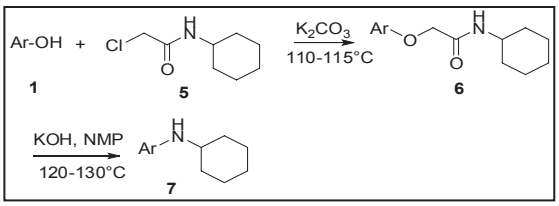
2. RESULT AND DISCUSSION

In order to demonstrate the versatility the method we describe the preparation of different aryl anilines such as N-t-butyl anilines, and N-cyclohexylanilines in good yields (Figure 2).

Recent method for the synthesis of t-butyl anilines [11] involves high-pressure reaction of anilines with isobutylene. In this report, we summarize a simple method for the preparation of N-t-butyl anilines

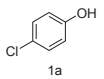
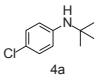
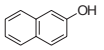
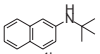
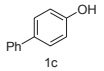
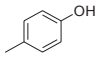
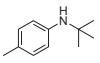


Scheme 1: Synthesis of N-1-cyclobutyl aniline.



Scheme 2: Synthesis of N-1-cyclohexyl aniline.

Table 1: Synthesis of N-1-cyclobutyl aniline[a,b].

S. No	Alcohol	Amine	Yield
1	 1a	 4a	82
2	 1b	 4b	76
3	 1c	 4c	66
4	 1d	 4d	87
5	 1e	 4e	76
6	 1f	 4f	87
7	 1g	 4g	90

[a]Yields calculated on the basis of the recovered starting phenol. [b]Isolated yield

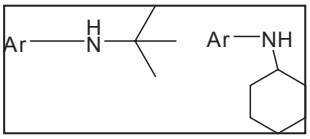
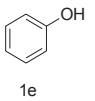
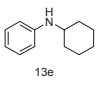


Figure 2: Structures of substituted anilines.

Table 2: Synthesis of *N*-1-cyclohexyl aniline[a,b].

S. No	Alcohol	Amine	Yield
1	 1a	 13a	72
2	 1b	 13b	75
3	 1c	 13c	68
4	 1d	 13d	88
5	 1e	 13e	84
6	 1f	 13f	89
7	 1g	 13g	78

[a]Yields calculated on the basis of the recovered starting phenol. [b]Isolated yield

using Smiles rearrangement as shown in Scheme 1. The yields are 60-90% over two steps, and the details are given in Table 1. Final amines are thoroughly characterized and reported.

Similarly N-1-cyclohexyl anilines are prepared using the same strategy as shown in Scheme 2. The data are given in Table 2, and anilines **7** are characterized completely.

3. CONCLUSION

A simple and efficient two-step green strategy for the synthesis of N-alkylarylamines was reported using amberlite IR-400 basic resin. This method produces a convenient, inexpensive, and scalable method of preparation of N-alkyl anilines.

4. ACKNOWLEDGMENT

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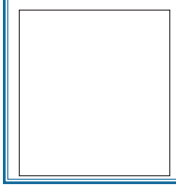
****Bibliographical Sketch***



Naveen Mulakayala earned his Ph.D. in chemistry from Sri Krishnadevaraya University, Anantapur, India. In 2008, he joined DR Reddy's Institute of Life Sciences, Hyderabad as a research associate with Dr. Manojit Pal and became research scientist in 2010. Naveen joined in AAP Pharma technologies as a Senior Research Scientist and then moved to Clearsynth Labs as a Principle Scientist.