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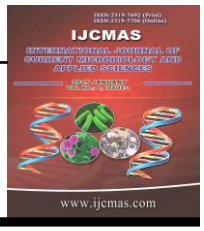

Original Research Article

A One-Pot Three Component Green Synthesis of 1-Aminoalkyl-2-Naphthols Using Grindstone Chemistry

M.Madan Mohan[1], CH.Santosh[1*] and A.Radhaiah[2]

[1]School of Life and Health Sciences, Adikavi Nannaya University, Rajahmundry-535105, A.P, India
[2]SVA Government Degree College for Men, Srikalahasti, Chittoor Dt, A.P, India
**Corresponding author*

Keywords

Green chemistry, 1-aminoalkyl-2-naphthols, Ortho quinines

A B S T R A C T

Among the several aspects of green chemistry, the substitution of volatile organic solvents with green solvents is of greatest apprehension. One of the most useful tools for the synthesis of chemically and biologically important compounds for their biological and pharmaceutical activities to treat differ health ailments at different trophic levels of chronic diseases. In this investigation an ecofriendly and proficient one-pot, three-component and simple synthesis of 1-aminoalkyl-2-naphthols via the reaction of aryl aldehydes, 2-naphthol and amine using 'Grindstone Chemistry' method is reported. This procedure is energy efficient and advantages of this method has operational simplicity, good yields of products in short reaction times, and practical applicability are easy work-up procedures.

Introduction

Consequent to the recently held World Climate Summit, green chemistry has more relevance internationally. In this circumstance, energy efficient, simple and rapid synthetic procedure suitable for mass scale operation is highly desirable. Many methods to prepare organic compounds involve toxic solvents and reagents. There is therefore a need to design cleaner synthetic procedures. With this view, Grindstone Chemistry is suitable both for desktop synthesis and kilogram scale operation also. To expend our effort toward environmentally benign synthesis, herein we wish to report a one-pot three-component reaction of 2-naphthol, aldehydes and amine catalyzed by methane sulphonic acid to afford 1-aminoalkyl-2-naphthols in excellent yields

The 'Grindstone Chemistry' is a slight modification of a process illustrated by Toda *et al* (1987) and showed that many reactions can be performed in high yields by simply grinding two or more solids together. Generally these reactions were carried out on a very small scale in an agate mortar and pestle. Tailored approach of 'Grindstone Chemistry' to chemical reactions on large scale was reported by Bose *et al* (2004).

Solvent-free chemicals reactions in high

yields can probably be conducted by grinding solid/solid, solid/liquid, or even liquid/liquid together (Bose *et al.*,2004;Babu *et al.*,2012 & Rao *et al*.,2012). For obtaining a better understanding of the energetics of the reaction, a thermocouple connected to a computer was used for recording the 'Reaction Temperature Profile' (change in the reaction temperature with the progression of time) during and after the grinding. Rise in temperature was observed during grinding which obviously reveals that the reaction is exothermic. Activation energy required for the reaction is provided by transfer of small amounts of energies of the reacting molecules through friction in solvent free condition, the reaction proceeds by itself if it is exothermic in nature; in contrast, grinding will not make the reaction go forward, if the reaction is endothermic. This is supported by the data from several of the successful reactions by grinding depicted by Tanaka (2003) and Rao *et al*.,(2010 a). Grinding process is made still more efficient by addition of friction-enhancing solids like $MgSO_4$.$7H_2O$ or sand according to the nature of reaction products, has given very satisfactory result in promoting the reaction between liquid reagents by the grinding method (Rao *et al*.,2010 b,Domling,2006 & Rao *et al*.,2011).

In recent times, 'Grindstone chemistry' is consistent with higher atom economy and green chemistry approach which has focused significant interest on multi-component reactions (MCRs), wherein at least three simple partners are added together to result in a single diverse complex structure which allow the formation of several new bonds (Jain *et al.*,2004;Zumpe *et al.*,2007;Nenajdenko *et al.*,2007;Valasani, 2014 & kumar *et al*,2014). Particularly in the last three decades a number of MCRs have been developed. Upshots like expediency and time saving by using 'Grindstone Chemistry' for small as well as large reactions is exemplified here by depicting the successful application of this method to the multi-component synthesis of 1- aminoalkyl-2-naphthols.

Materials and Methods

All chemicals were obtained from Sigma-Aldrich, Merck and Lancaster, and used as such without further purification. Melting points were determined using a calibrated thermometer by Guna digital melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded as solutions in DMSO-d_6 on a Bruker AMX 400 MHz spectrometer operating at 400 MHz for ^1H, 100 MHz for ^{13}C and tetramethylsilane as internal reference. LC Mass spectra were recorded on LCMS 2010A Shimadzu.

The reaction of 2-naphthols with aromatic aldehydes in the presence of *p*-TSA, wet-TCT, $HClO_4$-SiO_2 , $Yb(OTf)_3$, is known to give *ortho*-quinone methides (*O*-QMs), which have been used in the building up of dibenzoxanthene (Rao *et al*., 2010;Su W *et al*.,2008 & Khosropour *et al*.,2006). The same *O*-QMs, generated *in situ* have also been reacted with amides to form amidoalkyl naphthols (Valasani *et al*.,2013 (a&b)). *O*-QMs have an activated carbon-carbon double bond and have been used in many tandem processes. However, they have not been exploited sufficiently through their reactions with nucleophiles. We report herein the synthesis of aminoalkyl-2-naphthols via 'Grindstone Chemistry'.

Result and Discussion

Good results were attained in terms of yields and product purity in the presence of Methyl hydro sulfoxide ($MeSO_3H$), whereas, without $MeSO_3H$, the yields of products were reasonable after 20 minutes.

Significant changes in the yields were observed, when the reaction was carried out with aliphatic aldehydes such as formaldehyde and acetaldehyde. The reaction mixture showed the presence of a combination of starting material and numerous by-products in TLC and 1H NMR spectra, resulting in poor yields of the products (Vande *et al.*, 2002;Valasani,2014 a& b). Surprisingly, propanaldehyde, butyraldehyde and n-octanal did not work under the present protocol.

Synthesis of 1-aminoalkyl-2-naphthols in larger quantities was carried out on 0.25 M scale with reagent placed in a large porcelain bowl. The reaction mixture was ground with the help of a hand-held electric food mixer with stainless steel rotors for just under five minutes and the desired products were obtained in 83-95% yield. The reaction temperature profile as monitored by a thermocouple is shown in Figure 1. It is quite obvious that the aminoalkyl naphthol formation is exothermic. The increase in temperature for aminoalkyl naphthol formation with catalyst is 9.6^{o}C and without catalyst is 6.3^{o}C and the temperature difference is 3.3^{o}C. So we have concluded that the reaction is exothermic, as there was a rise in temperature in each case. In a pilot experiment, mixture of 2-naphthol (a) (0.204 g, 0.00142 mole), para-chloro benzaldehyde (b) (0.199 g, 0.00142 mole), and para-hydroxy aniline (c) (0.156 g, 0.00142 mole) in the presence of a catalytic amount of methane sulphonic acid (an inexpensive and readily available catalyst) was ground using a mortar and pestle of appropriate size (Scheme 1) at ambient temperature. Grinding for about 3 minutes led to a brown coloured solid of 4 in 95 % yield.

Subsequently, to outline the possibility of this approach principally by considering towards library building, this scheme was evaluated using 2-naphthol (a), substituted aldehydes (b), and para-hydroxy aniline (c). The consequent 1-aminoalkyl-2-naphthols were acquired in good yields under similar conditions. The reaction progresses rapidly under mild conditions and is compatible with a broad variety of functional groups. Earlier studies have also suggested that,synthesis of different pharmacologically important drug mmolecules through one plot and/or two pot synthesis produced 80-90% yield.(Reddy *et al*., 2011; Rao *et al*., 2013; Rao *et al.*, 2014; Vangavaragu *et al*., 2014 a &b; Rao *et al*., 2010 c).

The ^{1}H and ^{13}C NMR spectra of the products showed the formation of aminoalkyl naphthols. The nature of these compounds as 1:1:1 adducts was evident from their LCMS spectra, which exhibited, in each case, the molecular ion peak at the appropriate m/z value. Compounds **1-14** are stable solids whose structures were established by IR, ^{1}H and ^{13}C NMR spectroscopy and elemental analysis.

General procedure for the preparation of 1-((4-hydroxyphenyl amino) (phenyl) methyl) naphthalene-2-ol. (Entry **1**) is described as an example: A mixture of 2-naphthol (a) (0.204 g, 0.00142 mole), benzaldehyde (b) (0.145 g, 0.00142 mole), and *para*-hydroxy aniline (c) (0.156 g, 0.00142 mole) in the presence of a catalytic amount of methane sulphonic acid was ground using a motar and pestle of appropriate size. Grinding for about 3 minutes using a motar and a pestle of appropriate size. The initial syrupy reaction mixture solidified within 10 min. The solid was washed with water (20 mL) to afford the pure product in 87 % yield as a grey solid, mp = 248–250 ^{o}C. IR (KBr) (ν_{max}/cm^{-1}): 3324 (OH), 3212 (NH), (OH), 1670 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.52 (s, 1H), 8.61 (s, 1H), 7.49-7.50 (m,

3H), 7.74-7.76 (m, 3H), 7.88-7.91 (m, 9H), 7.20 (d, *J* = 9 Hz, 1H), 6.80 (d, *J* = 9 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.1, 156.3, 136.4, 130.8, 129.2, 128.7, 128.2, 127.5, 126.1, 122.6, 122.5, 118.5, 115.7, 108.6, 78.2, 54.2. APCI-MS: m/z (%) = 341(M^+). Anal.calcd for $C_{23}H_{19}NO_2$: C, 80.92; H, 5.61; N, 4.10. Found: C, 80.85; H, 5.57; N, 4.07.

Selected characterization data:

1-((2-hydroxyphenyl)(4-hydroxy-phenylamino) methylnaphthalene-2-ol (Entry 2): Dark brown solid, mp = 228-230 ^{o}C. IR (KBr) (ν_{max}/cm^{-1}): 3323 (OH), 3202 (NH), (OH), 1660 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.96 (s, 1H), 8.52 (s, 1H), 8.24 (s, 1H), 7.26-7.33 (m, 5H), 7.52-7.59 (m, 6H), 7.66-7.82 (m, 3H), 6.91 (d, *J* = 9.2 Hz, 1H), 5.19 (d, *J* = 9.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 153.4, 146.9, 141.2, 140.4, 133.8,131.1, 129.6, 128.8, 128.3, 126.4, 123.8, 118.9, 116.7, 116.5, 115.3, 54.2. APCI-MS: m/z (%) = 357(M^+). Anal. calcd for $C_{23}H_{19}NO_3$: C, 77.29; H, 5.36; N,3.92. Found: C, 77.24; H, 5.32; N, 3.87.

1-((4-hydroxyphenyl)(4hydroxyphenylamino)methyl)naphthalene-2-ol (Entry **3**): Yellow solid, mp = 251-253 ^{o}C. IR (KBr) (ν_{max}/cm^{-1}): 3326 (OH), 3216 (NH), (OH), 1665 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.90 (s, 1H), 8.67 (s, 1H), 8.65 (s, 1H), 7.77-7.60 (m, 4H), 7.55-7.36 (m, 4H), 7.27-7.06 (m, 5H), 6.94-6.74 (m, 1H), 6.63-6.58 (m, 1H) 6.51(d, *J* = 9.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 153.1, 146.4, 141.1, 140.2, 132.4, 130.0, 129.4, 128.2, 127.8, 126.4, 123.3, 118.8, 116.2, 116.3, 115.4, 54.1. APCI-MS m/z (%) = 357(M^+). Anal.calcd for $C_{23}H_{19}NO_3$: C, 77.29; H, 5.36; N, 3.92. Found: C, 77. 24; H, 5.32; N, 3.87.

1-((4-choro phenyl)(4-hydroxy-phenylamino) methyl) naphthalene- 2-ol (Entry 4): Brown solid, mp = 202-204 ^{o}C. IR (KBr) (ν_{max}/cm^{-1}): 3332 (OH), 3226 (NH), (OH), 1668 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.01 (s, 1H), 9.52 (s, 1H), 8.11-8.03 (m, 2H), 7.92-7,68 (m, 5H), 7.42-7.36 (m, 3H), 7.23-7.11 (m, 4H) 6.38 (d, *J* = 9 Hz, 1H), 5.90 (d, *J* = 9.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 153.6, 146.8, 142.9, 140.5, 133.7, 131.2, 129.3, 128.4, 128.3, 127.1, 124.1, 118.7, 117.4, 116.7, 114.4, 54.3. APCI-MS m/z (%) = 376(M^++H). Anal.calcd for $C_{23}H_{18}ClNO_2$: C, 73.50; H, 4.83; N, 3.73. Found: C, 73.46; H, 4.78; N, 3.69.

1-((2,4-dichlorophenyl)(4-hydroxyphenylamino)-methyl)naphthalene-2-ol (Entry **5**): Light green solid, mp = 198-200 ^{o}C. IR (KBr) (ν_{max}/cm^{-1}): 3336 (OH), 3204 (NH), (OH), 1662 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.86 (s, 1H), 8.97 (s, 1H), 8.14-8.05 (m, 3H), 7.90-7.66 (m, 4H), 7.37-7.32 (m, 2H), 7.20-7.09 (m, 4H) 6.53 (d, *J* = 8.3 Hz, 1H), 5.45 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 154.2, 146.8, 141.2, 140.1, 133.7, 131.8, 130.1, 129.4, 128.6, 128.1, 126.3, 123.5, 118.9, 116.3, 116.1, 115.2, 54.2. APCI-MS m/z (%) = 410 (M^++H). Anal.calcd for $C_{23}H_{17}Cl_2NO_2$: C, 67.33; H, 4.81; N, 3.41. Found: C, 67.27; H, 4.78; N, 3.37.

1-((4-diethylamino)-2-hydroxyphenyl) (4-hydroxyphenylamino) methyl) naphthalene-2-o1 (Entry **10**): Dark green solid, mp = 183-185 ^{o}C. IR (KBr) (ν_{max}/cm^{-1}): 3332 (OH), 3211 (NH), (OH), 1664 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.50 (s, 1H), 8.61 (s, 1H), 7.77 -7.66 (m, 3H), 7.40-7.05 (m, 8H), 6.79 (d, *J* = 8.3 Hz, 1H), 6.49- 6.41 (m, 2H), 6.06 (d, *J* = 8.3 Hz, 1H), 4.38 (s, 1H), 3.36 (q, 4H), 1.10 (t, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.1,

154.3, 148.5, 146.9, 140.2, 140.1, 133.5, 130.1, 129.8, 128.3, 126.1, 123.5, 118.9, 116.5, 116.1, 115.3, 115.2, 99.6, 48.7, 44.8, 13.1. APCI-MS m/z (%) = 428(M^+). Anal.calcd for $C_{27}H_{28}N_2O_3$: C, 75.68; H, 6.59; N, 6.54. Found: C, 75.63; H, 6.55; N, 6.50.

Table.1 Synthesis of 1-aminoalkyl-2-naphthol derivatives (1-14) using Grindstone Chemistry

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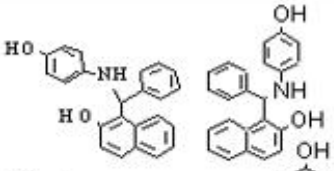
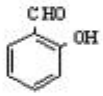
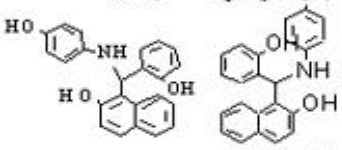
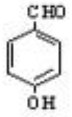
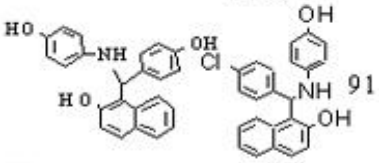
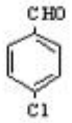
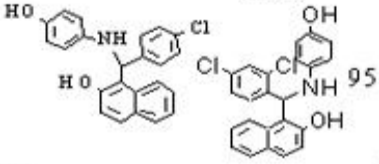
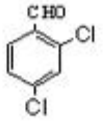
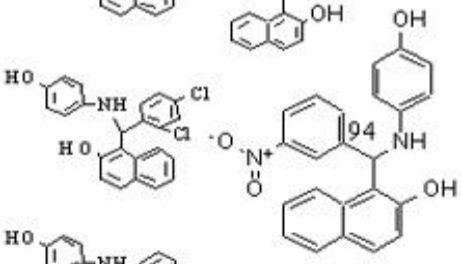
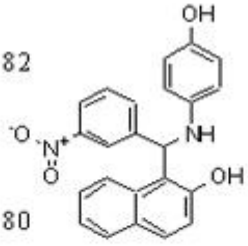
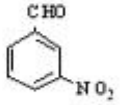
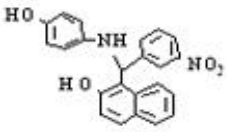
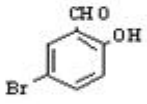
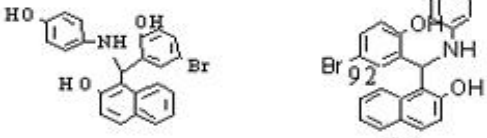
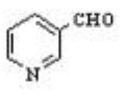
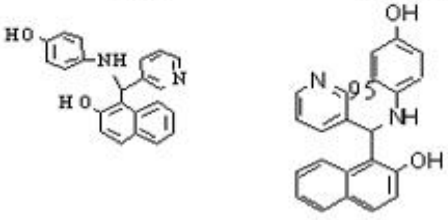
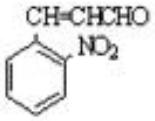
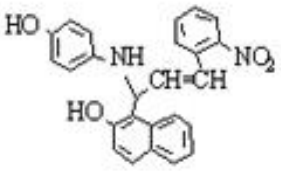
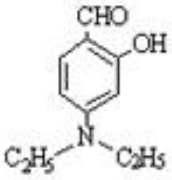
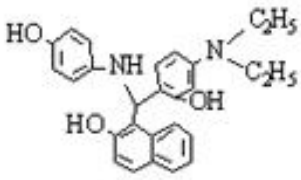
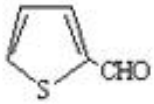
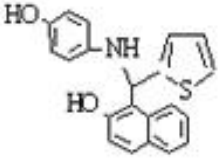
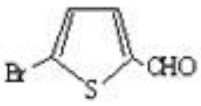
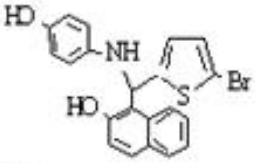
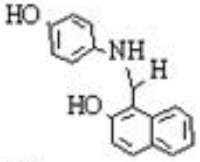
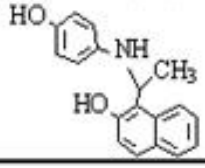
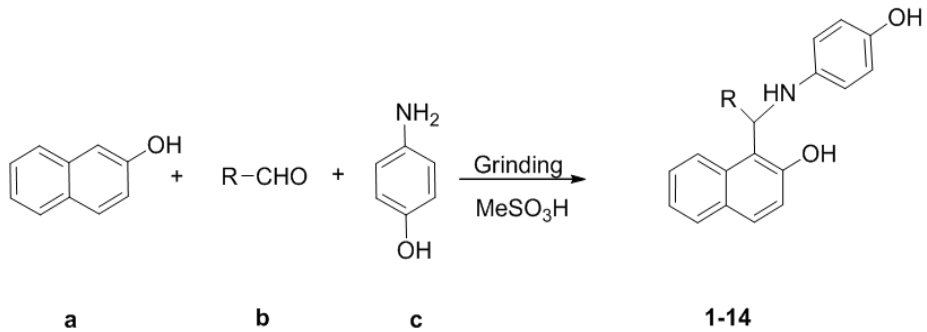
1			87	75
2			83	72
3			91	88
4			95	81
5			94	82 
6			91	80
7			92	80
8			95	83

Entry	Aldehyde	Product	Yield[a](%)	Yield[b](%)
9			84	71
10			89	76
11			89	77
12			90	81
13			20	–
14			35	

Scheme.1



Scheme.2 Suggested mechanism for the formation of aminoalkyl naphthols via conjugate addition reaction

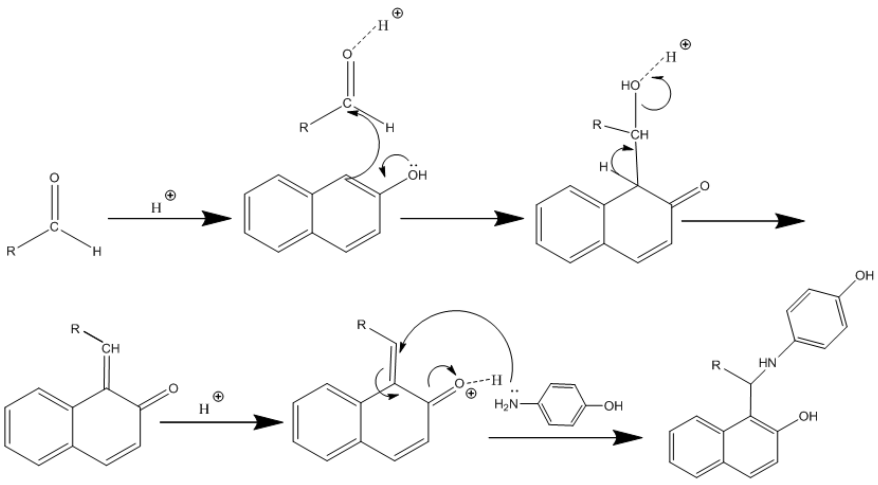
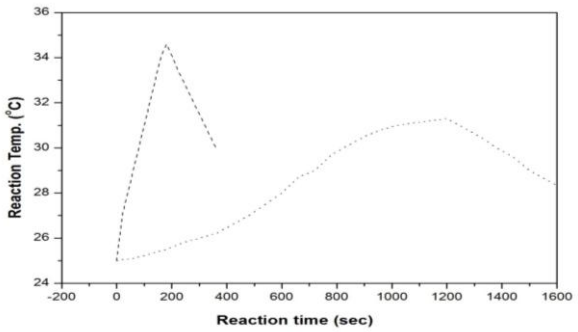


Figure.1 Reaction temperature profile (RTP) of amino alkyl naphthols formation with catalyst and without catalyst using Grindstone Chemistry



The structures of all the synthesized compounds were confirmed by elemental analysis and from spectral data (mass, ^{1}H, and ^{13}C NMR spectra).

The reaction of 2-naphthol with aromatic aldehydes in the presence of acid catalyst is known to give *O*-QMs *in situ* which have been reacted with aromatic amines to form 1-aminoalkyl-2-naphthol derivatives. A reasonable explanation for this result can be given by considering the nucleophilic addition to *O*-QM intermediate favourable via conjugate addition on the α, β-unsaturated carbonyl group and finally this intermediate will aromatize to produce the final aromatic compound. A plausible way of formation is shown in Scheme 2.

In conclusion, we have disclosed a simpler, faster, one-pot and three component method for the synthesis of 1-aminoalkyl-2-naphthols using 'Grindstone Chemistry'. This procedure is energy efficient and advantages of this method has operational simplicity, good yields of products in short reaction times and easy work-up procedures.

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