Microwave-Assisted One-Pot Synthesis of (Aminoalkyl)naphthols and (Aminoalkyl)quinolinols by Using Ammonium Carbamate or Ammonium Hydrogen Carbonate as Solid Ammonia Source

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Received 3 September 2008; revised 17 November 2008

Abstract: Ammonium carbamate and ammonium hydrogen carbonate were used as very effective solid ammonia sources to prepare different (aminoalkyl)naphthols and (aminoalkyl)quinolinols in ethanol and water as solvents under microwave conditions in modified three-component Mannich reactions. The products were obtained in excellent yields in one-pot reactions.

Key words: amino alcohols, green chemistry, heterocycles, Mannich bases, multicomponent reactions

In the past decade, modified three-component Mannich reactions, based on the aminoalkylation of 2- or 1-naphthol as the C–H acid, have become considerably important for the formation of C–C bonds under mild experimental conditions.[1] The syntheses of the aminonaphthols obtained in this way differ according to the nitrogen starting material: (a) by use of primary or secondary amines, secondary or tertiary aminonaphthols have been synthetized;[2–9] (b) with ammonia as source, primary aminonaphthols have been prepared.[10–15]

The areas of application of these aminonaphthols depend on the nature of the amino group; the enantiomers of secondary and tertiary aminonaphthols have been successfully applied as chiral catalysts in the enantioselective alkylation or arylation of benzaldehyde,[2–9] while primary aminonaphthols have been transformed into heterocyclic compounds,[10–12] subsequent condensation with different aldehydes furnishing interesting model compounds for examining the ring-chain tautomeric behavior of naphthoxazines.[13–18] On the other hand, the hypotensive and bradycardiac effects of 1-(aminomethyl)-2-naphthol derivatives have been evaluated,[18] and the syntheses of a wide variety of this type of compounds have recently been achieved through the hydrolysis of 1-(amidomethyl)-2-naphthols.[19]

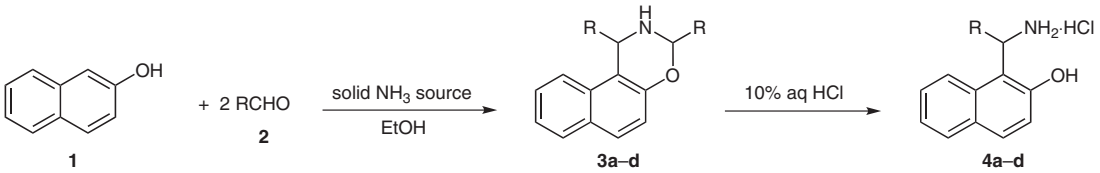
The overall yields of the desired aminonaphthols in the classical Betti reaction (starting from naphthol, methanolic ammonia, and the corresponding aldehyde, followed by acidic hydrolysis of the intermediate naphthoxazine) have been slightly improved by means of small modifications in the synthesis, e.g. by hydrolysis of the intermediate naphthoxazine without any workup, and by crystallization of the final aminonaphthol hydrochloride with ethyl acetate. However, the applications of these methods are still hampered by one or more disadvantages, such as the use of methanolic ammonia and unsatisfactory yields.

Since (aminoalkyl)naphthols have potential pharmacological activity, our present aim was primarily to improve the yields of these compounds and to increase the rates of the reactions by applying ammonium carbamate or ammonium hydrogen carbonate (as thermally decomposable solid ammonia sources) and microwave conditions in one-pot syntheses. Further aims were to extend this method to the preparation of new (aminoalkyl)naphthols and to use N-containing naphthol analogues such as quinolinols instead of naphthols.[15,17]

We began our study with the synthesis of 1-[amino(phenyl)methyl]-2-naphthol (**4a**) (Table 1). As the first step, we tested ammonium acetate and formate as solid ammonium sources in comparison to a methanolic ammonia solution. Microwave irradiation is often applied as green technology to prepare heterocyclic compounds[20] and Mannich-type products.[21–23] The discover mode (closed reaction conditions) of the CEM Discover LabMate microwave reactor combines the rapidity of the reaction under microwave conditions and the easy handleability of the reaction even at around 18–19 bar. Accordingly, the reaction was carried out in a 10-mL pressurized reaction vial with heating in a microwave reactor. The reactants were 2-naphthol, two equivalents of benzaldehyde, and two equivalents of the solid ammonia source. The two ammonium salts (ammonium acetate and formate) yielded **4a**, but the isolation of **3a** required aqueous workup, which defeated the aim of rapidity and one-pot handling of the reaction. Similar reaction results were obtained with several equivalents of ammonium carbamate, the ammonium salt of unstable carbamic acid (Table 1, entry 1). In contrast with other ammonium salts, the excess of ammonium carbamate or ammonium hydrogen carbonate formed in the reaction can be simply removed during evaporation of the reaction mixture above 60 °C.[24,25] The overall yield of **4a** could be increased up to 92%. In the next step, we investigated ammonium hydrogen carbonate as another inexpensive ammonia source that can be decomposed by heating of the reaction mixture.

SYNTHESIS 2009, No. 5, pp 0775–0778
Advanced online publication: 02.02.2009
DOI: 10.1055/s-0028-1083347; Art ID: T15508SS

Table 1 Reaction Conditions for the Preparation of (Aminoalkyl)naphthols **4a–d**



1 3a–d 4a–d

Entry	R	3	Conversion[a,b] (%)		4	Yield[c,d] (%)	
			A[e]	B[f]		A[e]	B[f]
1	Ph	**3a**	97	93	**4a**	92[g]	85[g]
2	2-thienyl	**3b**	95	91	**4b**	90	88
3	3-thienyl	**3c**	95	90	**4c**	88	91
4	*i*-Pr	**3d**	92	88	**4d**[h]	87[i]	90[i]

[a] Reagents and conditions: **1**, **2** (2 equiv), solid NH_3 source, EtOH, MW, 80 °C, 40 min.
[b] The conversion into **3** was determined from the NMR spectrum of the crude product.
[c] Reagents and conditions: **3**, 10% aq HCl, 100 °C, 90 min.
[d] The yield of **4** based on the starting naphthol **1**.
[e] Method A: $H_2NCO_2^-NH_4^+$ was used as the solid NH_3 source.
[f] Method B: $NH_4^+HCO_3^-$ was used as the solid NH_3 source.
[g] Ref. 13: 56% yield.
[h] Hydrolysis temperature 80 °C instead of 100 °C.
[i] Ref. 17: 80% yield.

The pressurized reaction vial proved excellent for following the reaction; for example, during the initial heating, the pressure was around 17–19 bar, which fell to 3–4 bar during the reaction, indicating the consumption of the ammonia. Ethanol was removed under reduced pressure, the temperature being kept at around 60 °C. A 10% hydrochloric acid solution was added to the residue and the suspension was heated. The water was removed under reduced pressure and the residue was crystallized from ethyl acetate. The synthesis method was tested for the reaction of three other aldehydes with 2-naphthol (Table 1, entries 2–4), including isobutyraldehyde to prepare **4d**, known from the literature.[17]

To test the scope and limitations of the method described above, we also used 1-naphthol as the C–H acid (Table 2, entries 1–4). All four aldehydes led to the formation of the desired (aminoalkyl)naphthols **7a–d** in good yields; for example, the yield of **7a** was increased from 57%[15] to 80% (Table 2, entry 1). Due to the relatively low reactivity of the N-containing naphthol analogues, there are few examples of their transformations in modified three-component Mannich reactions.[26–30] However, as a result of an integrated, virtual database screening, 7-[anilino(phenyl)methyl]-2-methyl-8-quinolinol was found to represent a promising new class of non-peptide inhibitors of the MDM2–p53 interaction.[31] Therefore, a further aim was to study the applicability of N-containing 1-naphthol analogues such as 8-quinolinol and 2-methyl-8-quinolinol in aminoalkylations with the corresponding aldehyde and ammonium carbamate as solid ammonia source. The reaction conditions, together with the yields, are listed in Table 2 (entries 5–8). It was concluded that aliphatic aldehydes (e.g., isobutyraldehyde), which are less reactive than aromatic ones, did not lead to the desired (aminoalkyl)quinolinols.

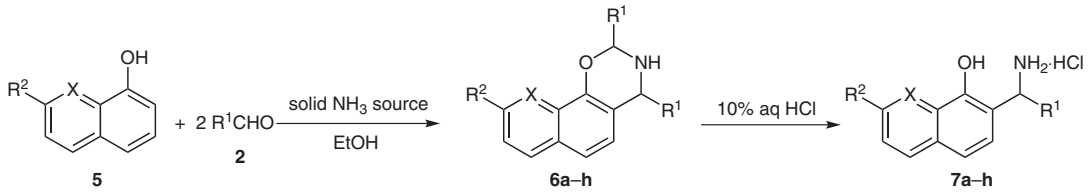
In conclusion, ammonium carbamate and ammonium hydrogen carbonate were applied as solid ammonia sources to prepare nine new (aminoalkyl)naphthol and (aminoalkyl)quinolinol derivatives in ethanol in good yields in one-pot three-component modified Mannich reactions. With this green methodology, three other (aminoalkyl)naphthols were synthesized. Depending on the solid ammonia source, the 56–80% yields obtained by using classical methodology (methanolic ammonia) could be increased to 87–92% or to 75–90%, and, simultaneously, the reaction times could be decreased.

Melting points were determined on a Kofler micro melting apparatus and are uncorrected. Elemental analyses were performed with a Perkin-Elmer 2400 CHNS elemental analyzer. Merck Kieselgel $60F_{254}$ plates were used for TLC. The ^1H and ^{13}C NMR spectra were recorded in DMSO-d_6 soln in 5-mm tubes, at r.t., on a Bruker Avance DRX400 spectrometer at 400.13 (^1H) and 100.61 (^{13}C) MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. Compounds **4a**,[13] **4d**,[17] and **7a**[15] are known from the literature.

Compounds 4b, 4c, and 7b–h; General Procedure

In a 10-mL pressurized reaction vial, the appropriate compound **1** or **5** (0.7 mmol), aldehyde **2** (2 equiv), and $H_2NCO_2NH_4$ (0.16 g, 2.1 mmol) were dissolved in EtOH (4 mL), and the reaction mixture was heated in a CEM Discover LabMate microwave reactor. The reaction conditions are listed in Tables 1 and 2. The solvent was removed under reduced pressure, the temperature being kept at around 60 °C. A 10% aq soln of HCl (4 mL) was added to the residue, and the mixture was heated (see Tables 1 and 2 for appropriate temperature). The H_2O was removed under reduced pressure and

Table 2 Reaction Conditions for the Preparation of (Aminoalkyl)naphthols **7a–d** and (Aminoalkyl)quinolinols **7e–h**



Entry	X	R^1	R^2	Temp[a] (°C)	Time[a] (min)	**6**	Conversion[a,b] (%)		Temp[c] (°C)	Time[c] (min)	**7**	Yield[c,d] (%)	
							A[e]	B[f]				A[e]	B[f]
1	CH	H	Ph	70	40	**6a**	87	85	80	60	**7a**	80[g]	75[g]
2	CH	H	2-thienyl	70	30	**6b**	80	82	80	30	**7b**	76	80
3	CH	H	3-thienyl	70	40	**6c**	85	87	80	60	**7c**	78	70
4	CH	H	*i*-Pr	70	40	**6d**	82	77	80	30	**7d**	70	76
5	N	H	Ph	130	45	**6e**	86	82	90	60	**7e**	72	78
6	N	H	3-thienyl	130	45	**6f**	82	75	90	60	**7f**	70	73
7	N	Me	Ph	130	45	**6g**	87	78	90	60	**7g**	75	80
8	N	Me	3-thienyl	130	45	**6h**	81	70	90	60	**7h**	73	68

[a] Reagents and conditions: **5**, **2** (2 equiv), solid NH_3 source, EtOH, MW, heat.
[b] The conversion into **6** was determined from the NMR spectrum of the crude product.
[c] Reagents and conditions: **6**, 10% aq HCl, 60 °C, 60 min.
[d] The yield of **7** based on the starting naphthol/quinolinol **5**.
[e] Method A: $H_2NCO_2^-NH_4^+$ was used as the solid NH_3 source.
[f] Method B: $NH_4^+HCO_3^-$ was used as the solid NH_3 source.
[g] Ref. 15: 57% yield.

the residue was treated with EtOAc; this gave **4b**, **4c**, and **7b–h** as beige or colorless crystals.

1-[Amino(2-thienyl)methyl]-2-naphthol Hydrochloride (4b)
Beige crystals; mp 184–187 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.11 (s, 1 H), 6.98 (t, *J* = 4.2 Hz, 1 H), 7.24–7.82 (m, 6 H), 7.81–7.99 (m, 2 H), 7.99 (d, *J* = 8.6 Hz, 1 H), 8.85 (br s, 3 H), 11.08 (br s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 48.1, 114.7, 119.4, 122.4, 123.9, 127.6, 127.7, 128.2, 128.4, 128.8, 129.6, 131.7, 132.2, 141.0, 154.4.

Anal. Calcd for $C_{15}H_{14}ClNOS$ (291.80): C, 61.74; H, 4.84; N, 4.80. Found: C, 61.85; H, 4.87; N, 4.81.

1-[Amino(3-thienyl)methyl]-2-naphthol Hydrochloride (4c)
Beige crystals; mp 201–204 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.24 (s, 1 H), 7.08–7.17 (m, 2 H), 7.27–7.35 (m, 2 H), 7.43–7.55 (m, 2 H), 7.83 (d, *J* = 8.6 Hz, 2 H), 8.02 (d, *J* = 8.8 Hz, 1 H), 8.76 (br s, 3 H), 10.89 (br s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 48.3, 114.6, 119.4, 122.6, 123.8, 124.5, 127.7, 127.9, 128.1, 128.9, 129.6, 131.4, 132.5, 139.1, 154.4.

Anal. Calcd for $C_{15}H_{14}ClNOS$ (291.80): C, 61.74; H, 4.84; N, 4.80. Found: C, 61.42; H, 4.81; N, 4.72.

2-[Amino(2-thienyl)methyl]-1-naphthol Hydrochloride (7b)
Beige crystals; mp 192–195 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.33 (s, 1 H), 7.41–7.61 (m, 6 H), 7.63 (d, *J* = 8.7 Hz, 1 H), 7.84–7.92 (m, 1 H), 8.34 (t, *J* = 4.2 Hz, 1 H), 9.06 (br s, 3 H), 10.19 (br s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 48.4, 120.0, 120.8, 123.5, 125.5, 126.0, 126.4, 127.5, 127.6, 127.9, 128.6, 130.2, 135.1, 141.9, 150.6.

Anal. Calcd for $C_{15}H_{14}ClNOS$ (291.80): C, 61.74; H, 4.84; N, 4.80. Found: C, 61.53; H, 4.86; N, 4.81.

2-[Amino(3-thienyl)methyl]-1-naphthol Hydrochloride (7c)
Beige crystals; mp 172–175 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.14 (s, 1 H), 7.19 (d, *J* = 4.1 Hz, 1 H), 7.41–7.61 (m, 6 H), 7.82 (d, *J* = 6.0 Hz, 1 H), 8.29 (d, *J* = 6.0 Hz, 1 H), 9.02 (br s, 3 H), 10.09 (br s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 49.2, 119.8, 120.9, 123.4, 124.3, 125.7, 126.1, 126.4, 127.6, 127.9, 128.1, 128.6, 130.3, 134.9, 150.6.

Anal. Calcd for $C_{15}H_{14}ClNOS$ (291.80): C, 61.74; H, 4.84; N, 4.80. Found: C, 61.62; H, 4.82; N, 4.78.

2-(1-Amino-2-methylpropyl)-1-naphthol Hydrochloride (7d)
Colorless crystals; mp 160–163 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.85 (d, *J* = 6.7 Hz, 3 H), 1.24 (d, *J* = 6.6 Hz, 3 H), 2.33–2.47 (m, 1 H), 4.66 (s, 1 H), 7.59–7.68 (m, 4 H), 7.99 (d, *J* = 6.0 Hz, 1 H), 8.43 (d, *J* = 6.3 Hz, 1 H), 8.49 (br s, 3 H), 9.97 (br s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 19.7, 20.4, 32.7, 55.1, 119.5, 120.7, 123.4, 125.7, 126.0, 126.1, 127.3, 128.5, 134.7, 151.1.

Anal. Calcd for $C_{14}H_{18}ClNO$ (251.75): C, 66.79; H, 7.21; N, 5.56. Found: C, 66.63; H, 7.28; N, 5.41.

7-[Amino(phenyl)methyl]-8-quinolinol Hydrochloride (7e)
Colorless crystals; mp 208–211 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.05 (q, *J* = 5.2 Hz, 1 H), 7.25–7.38 (m, 3 H), 7.47–7.55 (m, 3 H), 7.57–7.64 (m, 1 H), 7.78 (d, *J* = 8.7 Hz, 1 H), 8.38 (d, *J* = 8.2 Hz, 1 H), 8.88 (d, *J* = 4.0 Hz, 1 H), 9.19 (br s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 52.5, 118.9, 119.2, 121.7, 122.3, 123.4, 126.7, 128.2, 129.1, 129.2, 129.5, 138.1, 138.6, 139.0, 149.3, 150.5.

Anal. Calcd for $C_{16}H_{15}ClN_2O$ (286.76): C, 67.02; H, 5.27; N, 9.77. Found: C, 67.25; H, 5.31; N, 9.71.

7-[Amino(3-thienyl)methyl]-8-quinolinol Hydrochloride (7f)
Beige crystals; mp 197–200 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.14 (q, *J* = 4.9 Hz, 1 H), 7.24 (d, *J* = 5.0 Hz, 1 H), 7.52–7.58 (m, 2 H), 7.60 (s, 1 H), 7.66–7.72 (m, 1 H), 7.79 (d, *J* = 8.7 Hz, 1 H), 8.50 (d, *J* = 8.2 Hz, 1 H), 8.93 (d, *J* = 4.1 Hz, 1 H), 9.18 (br s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 48.7, 119.2, 122.3, 123.4, 124.6, 127.3, 127.9, 128.2, 129.4, 137.2, 139.2, 139.3, 148.8, 149.9.

Anal. Calcd for $C_{14}H_{13}ClN_2OS$ (292.78): C, 57.43; H, 4.48; N, 9.57. Found: C, 57.61; H, 4.41; N, 9.62.

7-[Amino(phenyl)methyl]-2-methyl-8-quinolinol Hydrochloride (7g)
Colorless crystals; mp 150–153 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.76 (s, 3 H), 6.09 (s, 1 H), 7.27–7.42 (m, 4 H), 7.48–7.79 (m, 4 H), 8.42 (d, *J* = 6.3 Hz, 1 H), 9.17 (br s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 23.7, 51.9, 117.8, 118.9, 121.8, 123.3, 123.8, 124.5, 125.8, 125.9, 127.6, 127.8, 129.0, 130.1, 142.8, 146.5, 158.6.

Anal. Calcd for $C_{17}H_{17}ClN_2O$ (300.78): C, 67.88; H, 5.70; N, 9.31. Found: C, 67.92; H, 5.74; N, 9.33.

7-[Amino(3-thienyl)methyl]-2-methyl-8-quinolinol Hydrochloride (7h)
Beige crystals; mp 210–212 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.81 (s, 3 H), 6.19 (s, 1 H), 7.23 (d, *J* = 5.1 Hz, 1 H), 7.52–7.62 (m, 3 H), 7.66 (d, *J* = 8.6 Hz, 1 H), 7.78 (d, *J* = 8.6 Hz, 1 H), 8.52 (d, *J* = 8.2 Hz, 1 H), 9.19 (br s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 23.8, 48.8, 113.8, 119.1, 121.0, 124.1, 124.2, 126.4, 126.5, 127.4, 127.8, 133.0, 139.1, 140.5, 158.8.

Anal. Calcd for $C_{15}H_{15}ClN_2OS$ (306.81): C, 58.72; H, 4.93; N, 9.13. Found: C, 58.63; H, 4.95; N, 9.11.

Acknowledgment

The authors' thanks are due to the Hungarian Research Foundation (OTKA No. K 75433) for financial support.

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