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# An improved procedure for amido alkyl naphthols: LiBr as a mild lewis acid alternative

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## ABSTRACT

An atom- efficient, environmentally benign and mild condition for the synthesis of amidoalkyl naphthols catalysed by substoichiometric amount of LiBr is described. Short reaction time, solvent free condition, simplicity of isolation and safe catalyst are the features.



## KEYWORDS

Aldehyde;
2-naphthol;
Acetamide;
Amidoalkylnaphthols;
LiBr;
Ortho-quinone methide(o-QM).

## INTRODUCTION

Multicomponent reactions (MCRs) are synthetic strategies of choice for chemists because of the inherent potential they have in generating molecular complexity in a single synthetic venture. The tremendous possibility for MCRs to describe novel reactions is greately acknowledged.[1] By efficiently approaching the criterias like-MCRs give target molecules in optimal yield while using as few steps as possible and giving as few side products as possible they become environmentaly benign processes.[2] The amount of research going on in this field and the broad scope is reflected in the fact that up to seven component reactions are reported.[3] Beautiful examples like Bigenilli, Ugi, Passerini, and Mannich reactions are some of the reactions which herald the synthetic utilities of the methodology. All the above qualities make MCRs superior tools for diversity oriented and complexity generating systems for drug discovery.[4]

1-amidoalkyl-2-naphthols are precursors for 1,3-amino-oxygenated functional motifs prepared by hydrolysis of amide or carbamate (in case of 1-carbamato-alkyl-2-naphthols). 1,3-amino-oxygenated functional motifs are common in a variety of biologically important natural products and potent drugs, including a number of nucleoside antibiotics and HIV protease inhibitors, such as ritonavir and lipinavir.[5] The hypotensive and bradycardiac effects of these compounds is also studied.[6] 1-amidoalkyl-2-naphthols are the molecular complexes generated by chemical transformations undergone by the three components viz 2-naphthol, aldehyde and amide Lewis acids or Bronsted acids as driving forces such as montmorillonite K10 clay,[7] $Ce(SO_4)$,[8] Iodine,[9] $K_5CoW_{12}O_{40}.\ 3H_2O$,[10] p-TSA,[11] sulfamic acid[12] cationic resins[13] and $P_2O_5$.[14] Several structural modifications are also done to increase the usefulness of these compounds. Ureas, substituted ureas and carbamates are also used instead of simple amide

or acetonitrile to get amido alkyl naphthols[13] and carbamato alkyl naphthols.[15] However many of these protocols suffer from drawbacks such as prolonged reaction time, use of highly acidic and highly hygroscopic reagents and chlorinated solvents. In the background of amidoalkyl naphthols being potential biologically active compounds development of newer methodologies using mild catalysts and solvent free conditions is a welcome goal. Lithium Bromide is a chemical compound of lithium and bromine, density 3.464g/cm is a versatile reagent in organic synthesis. As a stable and relatively safe compound, lithium, lithium bromide is used in various organic transformations. Efficiently it is serving as a unique, mild Lewis acid and neutral alternative for several important organic transformations.[16-22] In exploration of a new synthetic approach to amidoalkynaphthols herein we report an efficient, solventfree synthesis of amidoalkynaphthols catalysed by LiBr as mild catalyst. To the best of our knowledge there are no reports on the use of LiBr as catalyst for the synthesis of amidoalkylnaphthols. It has various advantages due to its nontoxicity, ease and safety in handling low cost and water solubility.

## EXPERIMENTAL

All the chemicals used are of commercial grade and were used without further purification. The products were characterized by comparison of their physical data with those of known samples or by comparison of their IR, $^1$H NMR, and LC-mass spectra

### General procedure for the synthesis of of amidoalkyl naphthols

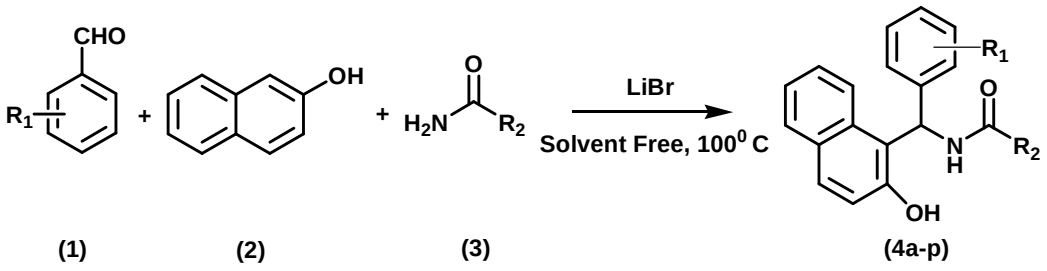
A mixture of 2-naphthol (1 mmol), benzaldehyde (1 mmol), acetonitrile (5 ml) and LiBr (30 mole%) heated to 100$^0$C for 4 hrs. The completion of reaction was monitored by TLC analysis. After the completion of the reaction the reaction mixture cooled to room temperature and acetonitrile removed under vaccum and directly loaded on to column and purified.

### N-[(4-Nitro-phenyl)-(2-hydroxy-naphthalen-1-yl)-methyl]-acetamide (4b)

Solid; Yield: 82%; m.p. 240-245$^0$C; IR (KBr) ícm$^{-1}$: 3390, 3265, 2594, 1644, 1601, 1522, 2900, 1436, 1065,830,735,448; $^1$H NMR (400 MHz, DMSO-$d_6$) äppm: 2.00 (s, 3H), 7.19 (d, *J*=8.0Hz, 1H), 7.22 (d, *J*=8.8Hz 1H), 7.27 (d, *J*=7.4 Hz 1Hz), 7.44 (t, *J*=7.4Hz, 1H), 7.54-7.60 (m 2H), 7.79 (t, *J* = 9.3Hz, 2H), 7.85 (d, *J*=7.0 Hz, 1H),7.99 (m, 2H), 8.59(d, *J*=8.0Hz, 1H); $^{13}$C NMR äppm: 22.3, 47.3, 115.5, 118.4, 119.5, 120.1, 121.1, 125.2, 127.4, 129.1, 131.1, 132.0, 132.9, 144.9, 146.9, 152.4, 168.9 ppm; Anal. Calcd for $C_{19}H_{16}N_2O_4$: C 67.85%, H 4.79%, N 8.33; Found: C 67.90, H 4.70, N 8.22.

## RESULTS AND DISCUSSION

Herein we wish to describe our study of LiBr as novel catalyst for the synthesis of amidoalkylnaphthols and optimization of the reaction conditions and the advantages over the catalysts previously used to achieve the synthesis of these compounds (Scheme 1)




**Scheme 1**

A mixture of 4-nitrobenzaldehyde, 2-naphthol and acetamide heated to 100$^0$ C in presence of 20 mole % LiBr initially to check whether the required product will be formed. The reaction completed in 1 hr with 85% product as shown by LCMS. Same set of starting materials were selected as model sub-

strates and we started to study the reaction in terms of temperature and catalyst loading to get optimum yield. We started with 5 mole % of catalyst and increase gradually. The observations with 4 different loadings is tabulated in TABLE 1. From the table it is evident that 30 mole % of catalyst is required to get maximum conversion.

**TABLE 1 : Study on the amount of catalyst required for maximum yield of 1-amidoalkyl-2-naphthols**

| Entry | Temp ($^0$C) | Time (hrs) | Yield (%)[a] |
|---|---|---|---|
| 1 | 100 | 1 | 90 |
| 2 | 90 | 1 | 84 |
| 3 | 80 | 1 | 77 |
| 4 | 110 | 1 | 89 |

[a]isolated yield.

We switched over the study in optimizing the reaction with respect to temperature. When we decreased the temperature below $100^0$ C the conversion started reducing. Increasing the temperature by $10^0$ C did not increase the yield. The results are summerised in TABLE 2. From the tables (TABLES 1&2) it is evident that we can get maximum yield of the product when we use 30 mole % of LiBr and when temperature was kept $100^0$ C.

In order to check the generality of the method we subjected various aromatic aldehydes containing electron withdrawing and electron donating substituents in ortho, meta or para positions. All the aldehydes reacted smoothly to give corresponding amidoalkyl naphthols in excellent yields (4a-x, TABLE 3). Unfortunately aliphatic aldehydes did not react to give the corresponding amidoalkyl naphthols. After the reaction is over water was added, stirred and filtered to wash away excess acetamide and the catalyst. The residual solid was recrystallised with ethanol to give pure amidoalkyl naphthols.

**TABLE 2 : Study on the optimum temperature required for maximum yield of amidoalkyl naphthols**

| Entry | Catalyst (mole%) | Time (hrs) | Yield (%)[a] |
|---|---|---|---|
| 1 | 30 | 1 | 90 |
| 2 | 20 | 2 | 85 |
| 3 | 10 | 3 | 75 |
| 4 | 5 | 4 | 66 |

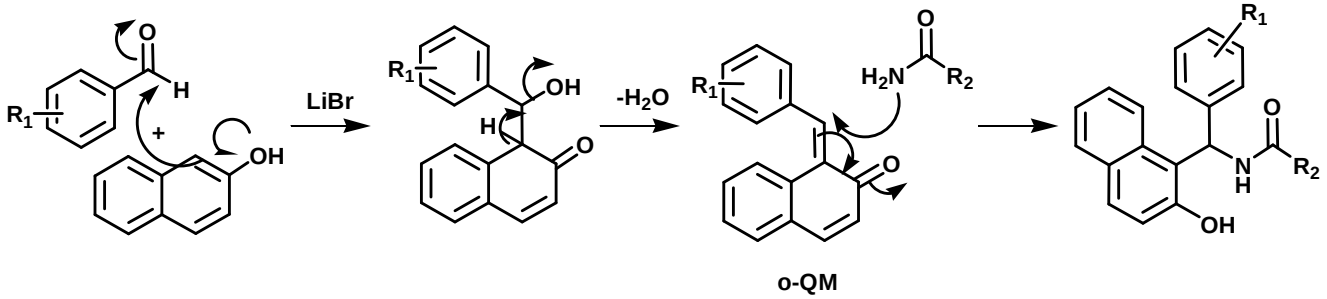
[a]isolated yield.

Mechanistically (Scheme 2) the reaction is rationalized to proceed with the intermediate ortho-quinone methide(o-QM) which is formed by nucleophilic addition of 2-naphthol to aldehyde catalysed by LiBr. Subsequent Michael addition of o-QM with the amide afforded the required amidoalkyl naphthols.

**TABLE 3 : LiBr catalyzed simple and efficient synthesis of amidoalkyl naphthols**

| Entry | $R_1$ | $R_2$ | Product[a] | Time (hrs) | Yield (%)[b] | Mp ($^0$C) | |
|---|---|---|---|---|---|---|---|
| | | | | | | Observed | Reported |
| 1 | H | $CH_3$ | 4a | 1 | 83 | 239-240 | 245-246 |
| 2 | 4-$NO_2$ | $CH_3$ | 4b | 1 | 82 | 240-245 | 248-250 |
| 3 | 3-NO2 | $CH_3$ | 4c | 1 | 82 | 239-241 | 241-242 |
| 4 | 2-NO2 | $CH_3$ | 4d | 1 | 83 | 181-183 | 180-182 |
| 5 | 4-Cl | $CH_3$ | 4e | 1 | 84 | 226-230 | 224-227 |
| 6 | 2-Cl | $CH_3$ | 4f | 1 | 83 | 209-210 | 213-215 |
| 7 | 4-MeO | $CH_3$ | 4g | 1 | 80 | 170-173 | 183-185 |
| 8 | 2-MeO | $CH_3$ | 4h | 1 | 85 | 243-245 | 241-242 |
| 9 | 4-Me | $CH_3$ | 4i | 1 | 82 | 224-225 | 222-223 |
| 10 | 4-$NO_2$ | $C_6H_5$ | 4j | 1 | 80 | 227-228 | 228-229 |
| 11 | 3-NO2 | $C_6H_5$ | 4k | 1 | 83 | 242-242 | 242-243 |
| 12 | 2-NO2 | $C_6H_5$ | 4l | 1 | 82 | 265-267 | 266-267 |
| 13 | 4-Cl | $C_6H_5$ | 4m | 1 | 81 | 169-170 | 168-170 |
| 14 | 2-Cl | $C_6H_5$ | 4n | 1 | 84 | 285-287 | 284-285 |
| 15 | 4-MeO | $C_6H_5$ | 4o | 1 | 80 | 205-208 | 206-208 |
| 16 | 2-MeO | $C_6H_5$ | 4p | 1 | 79 | 265-268 | 266-267 |

[a]All products were characterized by $^1$H NMR, $^{13}$C NMR and IR spectroscopic data and their m.p. compared with literature values[12,14,15]; [b]isolated yield




Scheme 2 : Tentative mechanism showing the formation of amidoalkyl naphthols

## CONCLUSION

In conclusion, a reliable, rapid, and environmentally benign method for the synthesis of 1-amidoalkyl-2-naphthols has been developed, which involves the use of substoichimetric amount of lithium bromide. In addition to the purity of the products, the short duration and ease of work-up make the method advantageous.

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