Synthesis of 4-alkoxy-*N*-substituted-1,8-naphthalimides

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The present work deals with two improved methods for the synthesis of 4-alkoxy-*N*-alkyl-1,8-naphthalimides from 4-nitro-*N*-alkyl-1,8-naphthalimides employing *in situ* generation of the alkoxylating agent in the alcoholic saturated solution of alkaline metal carbonates.

Keywords: ether–naphthalimides, sonochemistry, sonochemical effect on S_NAr

Thermochemical classic nucleophilic aromatic substitution reactions[1] (S_NAr) and other reactions involving photochemically,[2] electrochemically[3] or sonochemically[4] induced nucleophilic displacement on the aromatic nucleus have been known for long time with applications in the synthesis of dyes[5] and polymers[6].

Nucleophilic substitution of the aromatic nitro group can be achieved when it is activated by the presence of electron-withdrawing substituents in the *para* or *ortho* positions. The activating groups are arranged in the following series of decreasing efficacy:[6]

$$RCN > (RCO)_2NR' > RCOR' > RCO_2R'$$

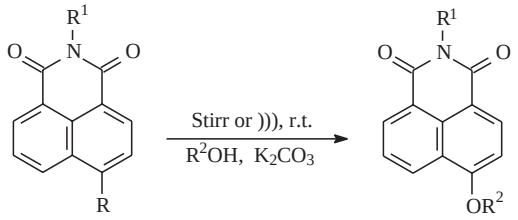
The general mechanism follows an addition–elimination pattern, passing through an anionic 1,1-σ-complex referred to as a Meisenheimer complex.[1g]

Naphthalenic moieties bearing nitro groups undergo also rapid substitution when properly activated. Good examples are the nitronaphthalic anhydrides and nitronaphthalimides which undergo S_NAr with amines in dipolar aprotic solvents such as DMSO, DMF and NMP.[7]

The 4-alkoxy-1,8-naphthalimides, luminophores known for their technological applications,[8] have been obtained from naphthalimides substituted at the 4-position by electron-withdrawing groups by many procedures. Most of the synthetic methods for preparation of 4-alkoxy-1,8-naphthalimides are based on S_NAr of halogens at the C-4 position by alkoxylating agents in dipolar aprotic solvents as *N*-methylpyrrolidinone (NMP), DMF and quinoline.[9] Other described methods use the alcohol itself as a solvent for the respective alcoholate.[10] These reactions are carried out under reflux at atmospheric or higher pressures up to 10 atm. Catalysts such as potassium or copper acetates are commonly used. Alkylation of hydroxy groups attached to the naphthalene moiety is also used for the synthesis of ether-naphthalimide compounds.[11]

Here we describe the reaction of 4-nitro-*N*-alkyl-1,8-naphthalimides with alkoxides, generated *in situ* by potassium carbonate and bicarbonate, under stirring at room temperature (silent mode) and sonochemical conditions (Scheme 1). The reactions were carried out in carbonate saturated solutions of hydrated alcohols. Both methods gave practically quantitative yields for 4-methoxy and 4-ethoxy naphthalimides (Table 1), no matter the nature of the *N*-substituent. In general, the sonochemical method displayed a two fold increase of the reaction rates, in agreement with the reported sonochemical effect on heterogeneous ionic reactions, showing no evidence for sonochemical switching.[12]

Since the alcohols employed were themselves poor nucleophiles, bearing almost the same nucleophilicity constants,[13] we concluded that the alcoholate should be



Scheme 1 Stirring or sonication conditions for alkoxy-naphthalimides formation. R^2 = Me, Et; R = NO_2.

Table 1 Reaction times and yields with (A) and without (B) sonication

Entry	R^1	R^2	Time/h A[a]	Time/h B[b]	Yield/%[c]
1a	Me	Me	4	2	97
1b	Me	Et	6	3	92
1c	nBu	Me	4	2	98
1d	nBu	Et	6	3	94
1e	Allyl	Me	4	2	98
1f	Allyl	Et	6	3	95

[a]Without sonication, [b]With sonication.

generated by carbonate[14] and bicarbonate alcoholysis, in as much, as their solubility in the media seems to play an important role. In addition, there was no contribution from the solid/liquid interface on these studied nucleophilic reactions, since, even under sonication conditions, there was no detectable product formation when the insoluble lithium carbonate was used.

The general reaction scope was further investigated with other common bases like sodium hydroxide, triethylamine, pyridine and other alkaline metal carbonate salts. It was found that the reaction did not occur with lithium carbonate, as mentioned earlier, and that the reactivity with different carbonates followed the order $Na^+ < K^+, C^{2+}$. Sodium hydroxide furnished the corresponding hydroxide naphthalimide derivative and alkoxides substitution products in an overall lower yield. With triethylamine as the base, the yields were poor and the reaction sluggish. Pyridine was a too weak base to promote the reaction at all.

Finally, with propanol, *n*-butanol and *t*-butanol only a trace of products was obtained, maybe owing to unreactive ion pair formation,[15,16] precluding thus an efficient attack and giving only trace of products after long reaction time under both conditions.

In the reaction with the isopropoxide the reaction mixture reddened after one hour under agitation and stayed unchangeable under sonication. While, the sonicated solution turned red after standing for a few minutes, giving no isolable product.

In comparison with other literature procedures[10] for the synthesis of 4-methoxy-*N*-methyl-1,8-naphthalimide **1a** (reflux in MeOH, $CuSO_4.5H_2O$, NaOMe, 12 hours) our method has the advantages of being faster, employing mild

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conditions, having an easy work-up, and giving surprisingly excellent yields (Table 1, R_1=Me, Allyl, *n*-butyl).

Experimental

4-Nitro-*N*-substituted-1,8-naphthalimides were synthesised from anhydrides and corresponding amines by a sonochemical route.[17] The corresponding naphthalimide (1×10^{-3} moles) was dissolved in MeOH (35 ml) and EtOH (60ml) with 10 equivalents of potassium carbonate. The sonication reactions were carried out in an ultrasonic cleaner bath (Bransonic 150W/ 25KHz output) within a cylindrical reaction vessel of 40 mm diameter. Stirred reactions were run in an 100 ml Erlenmeyer flask. All reactions were monitored by TLC. At the end of the reaction, the solvent was removed *in vacuo*, the residue was dissolved in $CHCl_3$ and the solution was washed successively with 10% aqueous sodium hydroxide and water and then dried and evaporated. Melting points were determined in a electrothermal melting point apparatus. R_f values were determined on Merck silica gel plates with fluorescent indicator (254nm) and CH_2Cl_2 eluent. The ^{1}H NMR spectra were recorded on a Bruker AC-200 (in $CDCl_3$). The IR spectra were registered on a BOMEM-FTIR MB 102 spectrophotometer in the range between 300 and 4000cm^{-1}, KBr pellets. Capillary GC analyses were performed on a HP-5890 coupled to a MSD-5970 mass selective detector. Elemental analyses were determined on a CE Instruments EA 1110 CHNS-O Elemental Analyzer.

4-methoxy-N-methyl-1,8-naphthalimide **1a**: pale yellow needles; m.p. 197–198°C (literature[10] = 197–201°C); R_f = 0,21 (CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 3.5 (s, 3H, N–CH_3), 4.0 (s, 3H, O–CH_3), 7.0 (d, *J*=8.2 Hz, 1H, Ar), 7.6 (t, *J*=8.2 Hz, 1H, Ar), 8.5 (m, 3H, Ar); MS (*m/z)* 241(M^+,100), 213, 198, 182, 113; IR (KBr) 3021, 2945, 1698, 1658, 1580, 1356, 1254, 1077cm^{-1}; anal. calcd for $C_{14}H_{11}NO_3$: N, 5.81; C, 69.70; H, 4.60. Found: N, 5.86; C, 69.68; H, 4.63.

4-ethoxy-N-methyl-1,8-naphthalimide **1b**: pale yellow needles; m.p. 173–174°C (literature[18] = 173–175°C); R_f = 0,28 (CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.6 (t, *J*=7.0 Hz, 3H, CH_3), 3.5 (s, 3H, N–CH_3), 4.3 (quartet, *J*=7.0 Hz, 2H, CH_2), 6.9 (d, *J*=8.2 Hz, 1H, Ar), 7.6 (t, *J*=8.2 Hz, 1H, Ar), 8.5–8.6 (m, 3H, Ar); MS (*m/z*) 255, 227(M^+,100), 199, 183, 115; IR (KBr) 3021, 2945, 1699, 1656, 1355, 1072cm^{-1}; anal. calcd for $C_{15}H_{13}NO_3$: N, 5.49; C, 70.58; H, 5.13. Found: N, 5.43; C, 70.62; H, 5.14.

4-methoxy-N-butyl-1,8-naphthalimide **1c**: pale yellow needles; m.p. 114–115°C (literature[18] = 115–116°C); R_f = 0,25 (CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.9 (t, *J*= 7.0 Hz, 3H, CH_3), 1.3–1.8 (m, 4H, 2CH_2), 4.1 (s, 3H, O–CH_3), 4.2 (t, 2H, N–CH_2), 7.0 (d, *J*=8.2 Hz, 1H, Ar), 7.7 (t, *J*=8.2 Hz, 1H, Ar), 8.4–8.6 (m, 3H, Ar); MS (*m*/*z*) 283, 227(M^+,100), 210, 184, 113; IR (KBr) 3028, 2952, 1698, 1659, 1354, 1257, 1080cm^{-1}; anal. calcd for $C_{17}H_{17}NO_3$: N, 4.94; C, 72.07; H, 6.05. Found: N, 4.93; C, 72.01; H, 6.10.

4-ethoxy-N-butyl-1,8-naphthalimide **1d**: pale yellow needles; m.p. 132–133°C (literature[18] = 133–134°C); R_f = 0,55 (CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.0 (t, *J*=6.7 Hz, 3H, CH_3), 1.3–1.8 (m, 7H, 2CH_2 and CH_3), 4.2 (t, *J*=6.6 Hz, 2H, N–CH_2), 4.3 (quartet, 2H, *J*=6.9 Hz, CH_2), 7.1 (d, *J*=8.3 Hz, 1H, Ar), 7.6 (t, *J*=8.3 Hz, 1H, Ar), 8.4–8.6 (m, 3H, Ar); MS (*m*/*z*) 297, 241, 213(M^+,100), 196, 113; IR (KBr) 3032, 2957, 1701, 1658, 1357, 1256, 1081cm^{-1}; anal. calcd for $C_{18}H_{19}NO_3$: N, 4.71; C, 72.71; H, 6.44. Found: N, 4.77; C, 72.67; H, 6.48.

4-methoxy-N-allyl-1,8-naphthalimide **1e**: pale yellow needles; m.p. 119–120°C (literature[19] = 119–120°C); R_f = 0,45 (CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 4.1 (s, 3H, O–CH_3), 4.7 (d, 2H, N–CH_2), 5.2–5.3 (dd, *J*=17,1 Hz, *J*=10.2 Hz, 2H, CH_2), 5.9–6.0 (m, 1H, CH), 7.0 (d, *J*=8.2 Hz, 1H, Ar), 7.7 (t, *J*=8.2 Hz, 1H, Ar), 8.5-8.6 (m, 3H, Ar); MS (*m/z*) 267(M^+), 252(100), 237, 184, 113; IR (KBr) 3026, 2946, 1701, 1665, 1582, 1356, 1253, 1075cm^{-1}; anal. calcd for $C_{16}H_{13}NO_3$: N, 5.24; C, 71.90; H, 4.90. Found: N, 5.29; C, 71.82; H, 4.92.

4-ethoxy-N-allyl-1,8-naphthalimide **1f**: pale yellow needles; m.p. 130–131°C (literature[19] = 131–133°C); R_f = 0,49 (CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.2 (t, *J*=7.0 Hz, 3H, CH_3), 3.7 (quartet, *J=7.*0 Hz, 2H, CH_2), 4.7 (d, 2H, N–CH_2), 5.2-5.3 (dd, *J*=17,1 Hz, *J*=10.2 Hz, 2H, CH_2), 5.9–6.0 (m, 1H, CH), 7.0 (d, 1H, Ar), 7.7 (t, 1H, Ar), 8.5–8.6 (m, 3H, Ar); MS (*m/z*) δ 281(M^+), 255, 227(100), 183, 115; IR (KBr) 3022, 2954, 1701, 1668, 1585, 1353, 1252, 1078cm^{-1}; anal. calcd for $C_{17}H_{15}NO_3$: N, 4.98; C, 72.58; H, 5.37. Found: N, 4.97; C, 72.51; H, 5.33.

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