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Ionic liquids accelerate access to N-substituted-1,8-naphthalimides

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ABSTRACT

The synthesis of N-substituted-1,8-naphthalimides is accelerated in the presence of the room temperature ionic liquid [BMIM][NO_3]. Reaction times are reduced from 18 h in volatile organic compounds (VOCs) ($PhCH_3$, EtOH and THF) to 20 min in the ionic liquid [BMIM][NO_3]. The reaction yields are typically increased to >85% and the products are isolated by ethanol-mediated precipitation direct from the ionic liquid, requiring no further purification.

Medicinal chemistry utilises robust, reliable procedures to access rapidly compounds for biological screening. It is this need for rapid compound access that delineates medicinal chemistry from synthetic chemistry. In one of our most recent programmes, we required access to focused libraries of substituted 1,8-naphthalimides of the type shown in Figure 1. This focused library approach is one that we have used with considerable success in the development of novel inhibitors of dynamin GTPases and of protein phosphatases 1 and 2A.[1–8]

Naphthalimides and their derivatives are well-known, and they demonstrate a wide variety of applications due to properties such as fluorescence, electroactivity and photostability. Naphthalimides find use as optical brighteners, daylight fluorescent pigments, solar energy collectors and fluorescent dyes for textiles and polymeric materials.[9] Derivatives of naphthalimide have also been reported as fluorescent molecular probes, anti-viral agents and anti-cancer agents.[10–12] Irradiation of brominated naphthalimide derivatives has been shown to generate photoproducts with strong anti-viral activity.[11] Naphthalimides are promising anti-cancer agents, showing broad spectrum activity against a range of murine and human tumour cells.[12] Their DNA binding and enzyme inhibitory activity are believed to be crucial to their anti-tumour effects. Several derivatives have reached various phases of clinical trials, showing promising results, but further progress has been prevented due to dose-limiting toxicity.[12] However, there is still a considerable amount of effort being expended in fine-tuning the anti-tumour activity of these analogues.[13–16]

Two well-established methods for the synthesis of N-substituted-1,8-naphthalimides have been described: N-alkylation of a 1,8-naphthalimide potassium salt with alkyl halides and a more general method involving condensation of an amine with 1,8-naphthalic anhydride under reflux.[17] Whilst both approaches are amenable to focused library development, they suffer the drawback of requiring forcing conditions and prolonged reaction times. Additionally, in our experience, it is often difficult to isolate the desired product from the reaction mixture. Given our prior experience in the use of room temperature ionic liquids (RTILs) for accelerating reactions, we sought to develop an expedient RTIL route to focused libraries of N-substituted-1,8-naphthalimides.[18–20] Our efforts are reported herein.

Our initial studies in this area examined the use of traditional volatile organic solvents (VOCs) under standard reaction conditions. In a model experiment, 1,8-naphthalic anhydride was treated with 1.1 equiv of 2-aminoethanol, and heated in various VOCs in a thick-walled reaction tube for 18 h (sealed tube reaction) (Scheme 1).[21] We evaluated the efficiency of the 2-aminoethanol addition using $PhCH_3$ (130 °C), EtOH (100 °C) and THF (85 °C) as

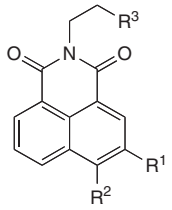

Figure 1. Generic structure of 3,4-substituted-1,8-naphthalimides.

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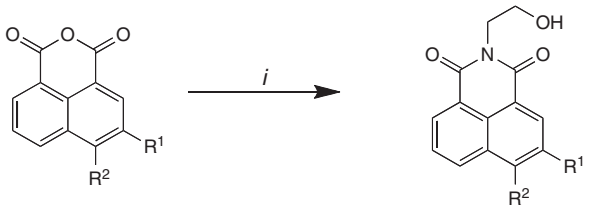
the reaction solvents. This allowed for a reasonable breadth of solvent type and reaction temperatures to be surveyed.

As can be seen from the data presented in Table 1, for the parent anhydride, the reaction proceeded well in both $PhCH_3$ and EtOH, with isolated yields of 85% and 81%, respectively (Table 1, entries 1 and 3). The corresponding reaction in THF afforded a disappointing yield of 40% (Table 1, entry 2). As such, further evaluations were confined to the use of $PhCH_3$ and EtOH as reaction solvents. Introduction of substituents to the naphthalene moiety had little effect on the isolated yield of product, with the 4-SO_3K, 4-Br and 4-Cl analogues obtained in yields of 61–84% (Table 1, entries 4–9). The 3-SO_3Na, 3-Br and 3-NH_2 derivatives were accessed with similar efficiency, with yields ranging from 71% to 86% (Table 1, entries 10–13). It is clear that EtOH is the solvent of choice in these transformations, suggesting a more favourable outcome with more polar solvents. Whilst the reaction yields are excellent, the reaction required 18 h at elevated temperatures.

Having established our benchmark reaction yields and conditions with VOCs, we next turned our attention to conducting our model reaction in two different room temperature ionic liquids (RTILs): [BMIM][NO_3] and [BMIM][BF_4]. The outcomes of these initial evaluations are presented in Table 2. Our observations after 18 h reaction time indicated complete conversion of the parent 1,8-naphthalic anhydride (not shown), and as we were keen to establish rapid access to these analogues, shorter reaction times were subsequently examined.

In a typical RTIL reaction, after 20 min at 140 °C, the mixture was allowed to cool and ethanol was added. This addition resulted in clean precipitation of the desired product which was collected by filtration and by both ^1H and ^{13}C NMR spectroscopy which required no further purification.



Scheme 1. Reagents and conditions. (i) 2-aminoethanol, Δ, solvent (see Table 1), 18 h.

Table 1
Isolated yields of 3,4-substituted-N-(2-hydroxyethyl)-1,8-naphthalimides from the reaction of substituted 1,8-naphthalic anhydrides with 2-aminoethanol in $PhCH_3$, THF and EtOH for 18 h

Entry	R^1	R^2	Solvent	T^a (°C)	Yield (%)
1	H	H	$PhCH_3$	130	85
2	H	H	THF	85	40
3	H	H	EtOH	100	81
4	H	Br	$PhCH_3$	130	70
5	H	Br	EtOH	100	82
6	H	Cl	$PhCH_3$	130	61
7	H	Cl	EtOH	100	84
8	H	SO_3K	$PhCH_3$	130	68
9	H	SO_3K	EtOH	100	74
10	SO_3Na	H	$PhCH_3$	130	71
11	SO_3Na	H	EtOH	100	75
12	Br	H	EtOH	100	86
13	NH_2	H	EtOH	100	78

[a] Reactions were carried out in a thick-walled sealed reaction vessel; temperature measured at the baseplate of a 12-position Radleys' carousel reaction station.[22]

Table 2
Isolated yields of 3,4-substituted-N-(2-hydroxyethyl)-1,8-naphthalimides from the reaction of substituted 1,8-naphthalic anhydrides with 2-aminoethanol in [BMIM][NO_3] and [BMIM][BF_4] at 140 °C[a]

Entry	R^1	R^2	Solvent	Time	Yield (%)
1	H	H	[BMIM][NO_3]	1 h	87
2	H	H	[BMIM][NO_3]	20 min	88
3	H	H	[BMIM][BF_4]	20 min	91
4	H	SO_3K	[BMIM][NO_3]	8 h	55
5	H	SO_3K	[BMIM][NO_3]	1 h	52
6	H	SO_3K	[BMIM][NO_3]	20 min	53
7	SO_3Na	H	[BMIM][NO_3]	20 min	85
8	H	Br	[BMIM][NO_3]	20 min	90
9	H	Cl	[BMIM][NO_3]	20 min	83
10	H	Cl	[BMIM][BF_4]	20 min	96
11	Br	H	[BMIM][NO_3]	20 min	90
12	NH_2	H	[BMIM][NO_3]	20 min	94

[a] Reactions were carried out in a thick-walled sealed reaction vessel at 140 °C; temperature measured at the baseplate of a 12-position Radleys' carousel reaction station.[22]

From examination of the data presented in Table 2, three features are immediately apparent. Firstly, the reactions were complete in a considerably shorter time than their VOC counterparts with all reactions being complete after 20 min. Secondly, excepting entries 4–6, the isolated yields were on average 5–10% higher than those observed in the equivalent VOC reaction. Thirdly, the 4-SO_3K analogue returned a very poor isolated yield, regardless of reaction duration or room temperature ionic liquid used.

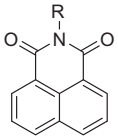
It is tempting to attribute the poor isolated yield of the 4-SO_3K analogue to difficulty in its isolation from the RTIL solvent, however, no such issue was noted with the analogous 3-SO_3Na compound. Whilst logically, this is the most rational reason for this observation, we were unable to supply direct evidence for this effect.

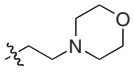
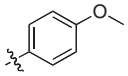
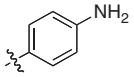
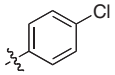
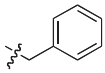
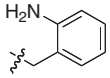
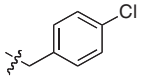
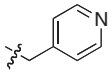
Given our desire to use this approach in the development of focused compound libraries, it was imperative that it was applicable across a broad spectrum of amines to allow access to the desired N-substituted-1,8-naphthalimides. To explore the scope of this approach, we examined the development of a highly focused library of eleven N-substituted-1,8-naphthalimides. This library encompassed simple aliphatic and heterocyclic amines as well as electron-donating and electron-withdrawing anilines.

As can be seen from the data presented in Table 3, the addition of a wide variety of amines to 1,8-naphthalic anhydride in [BMIM][NO_3] proceeds smoothly and in typically excellent yield (76–97%). Aliphatic and cyclic aliphatic amines are well tolerated (Table 3, entries 1 and 3) as are terminally substituted amines (Table 3, entries 2 and 4). Aromatic amines react as expected, with electron-donating anilines affording the highest isolated yields of 95–97%. The electron-withdrawing *p*-chloro analogue gave a disappointing 10–15% conversion (by ^1H NMR) after 20 min, however, extension of the reaction time to 3 h resulted in a 93% isolated yield (Table 3, entry 7). This is still a significant enhancement relative to the equivalent VOC reaction (3 vs 18 h). The *p*-chlorobenzyl analogue was generated in a 97% isolated yield after 20 min (Table 3, entry 10), strongly suggesting that the lower yield of the *p*-chloroanilino analogue is directly attributable to the low nucleophilicity of this amine. A similar conclusion can be drawn for the marginally lower yield observed with allylamine (76%, Table 3, entry 2).

In conclusion, we have reported that replacement of VOCs with the room temperature ionic liquid [BMIM][NO_3] has allowed for a significant reduction in the reaction time (from 18 h to 20 min), in all but one case, for the synthesis of a wide range of

Table 3
Isolated yields of N-substituted-1,8-naphthalimides from the reaction of 1,8-naphthalic anhydride with various amines in [BMIM][NO_3] at 140 °C[a]



Entry	R	Time	Yield (%)
1		20 min	90
2		20 min	76
3		20 min	92
4		20 min	89
5		20 min	95
6		20 min	96
7		3 h	93[b]
8		20 min	88
9		20 min	97
10		20 min	97
11		20 min	95

[a] Reactions were carried out in a thick-walled sealed reaction vessel at 140 °C; temperature measured at the baseplate of a 12-position Radleys' carousel reaction station.[22]

[b] 10–15% conversion by ^{1}H NMR spectroscopy after 20 min at 140 °C.

N-substituted-1,8-naphthalimides. This method is clearly applicable to the synthesis of focused libraries, and hence the development of new biologically active 1,8-naphthalimides. We will report our efforts in this latter area in due course.

Acknowledgements

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Supplementary data

Supplementary data (spectral data for novel products and references to various compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.12.015.

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21. *Synthesis of 1-butyl-3-methylimidazolium bromide, [BMIM][Br]*: To a clean, dry round-bottomed flask were added 1-methylimidazole (29.4 mL, 0.37 mol) and 1-bromobutane (44.1 mL, 0.41 mol). The reaction mixture was stirred at 70 °C for 24 h. During this time, an emulsion formed, followed by the formation of the colourless ionic liquid. The crude ionic liquid was washed with Et_2O (3 × 30 mL) to remove excess 1-bromobutane, then dried in vacuo (50 °C, 40 mbar) for ~2 h. On cooling to room temperature, the colourless, viscous ionic liquid crystallised to form a white solid. Yield: 74.1 g (92%); ^{1}H NMR (DMSO-d_6) δ 0.86 (3H, t, J = 7.2 Hz), 1.23 (2H, m), 1.74 (2H, m), 3.86 (3H, s), 4.19 (2H, t, J = 7.2 Hz), 7.78 (1H, t, J = 1.8 Hz), 7.86 (1H, t, J = 1.8 Hz), 9.36 (1H, t, J = 1.8 Hz); ^{13}C NMR (DMSO-d_6) δ 13.4, 18.9, 31.5, 35.9, 48.6, 122.4, 123.7, 136.7 ppm.
Synthesis of 1-butyl-3-methylimidazolium nitrate, [BMIM][NO_3]: To a stirring solution of 1-butyl-3-methylimidazolium bromide (65.7 g, 0.30 mol) in H_2O (100 mL) was added a solution of $AgNO_3$ (51.0 g, 0.30 mol) in H_2O (100 mL). A pale yellow precipitate of AgBr instantly formed. The reaction mixture was stirred for 2 h, then filtered twice to remove the AgBr by-product. The H_2O was removed in vacuo, resulting in the crude product, as a yellow viscous liquid. This was dissolved in MeCN (20 mL) and the resulting solution was filtered. The MeCN was evaporated, and the product dried in vacuo (50 °C, 40 mbar) for ~2 h to yield the pure ionic liquid as a pale yellow viscous liquid. Yield: 51.5 g (85%); ^{1}H NMR (DMSO-d_6) δ 0.86 (3H, t, J = 7.2 Hz), 1.23 (2H, m), 1.74 (2H, m), 3.84 (3H, s), 4.15 (2H, t, J = 7.2 Hz), 7.70 (1H, t, J = 1.8 Hz), 7.77 (1H, t, J = 1.8 Hz), 9.17 (1H, t, J = 1.8 Hz); ^{13}C NMR (DMSO-d_6) δ 13.5, 19.0, 31.6, 35.9, 48.8, 122.6, 123.9, 136.9 ppm.
Typical Synthesis of N-(2-hydroxyethyl)-1,8-naphthalimide in a VOC: 2-Aminoethanol (350 µL, 5.8 mmol) was added to a stirred suspension of 1,8-naphthalic anhydride (1.005 g, 5.1 mmol) in EtOH (20 mL). The resulting suspension was refluxed at 100 °C for 18 h, then cooled to room temperature. The precipitated product was collected by filtration, washed with EtOH and dried under vacuum. Where $PhCH_3$ was used as the solvent, three drops of Et_3N were added to reaction mixture. Mp 174–176 °C; ^{1}H NMR (DMSO-d_6) δ 3.61 (2H, m), 4.14 (2H, t, J = 6.6 Hz), 4.81 (1H, t, J = 6.0 Hz, OH), 7.85 (2H, dd, J = 7.5, 8.1 Hz), 8.44 (2H, dd, J = 0.9, 8.1 Hz), 8.47 (2H, dd, J = 0.9, 7.5 Hz); ^{13}C NMR (DMSO-d_6) δ 42.0, 58.0, 122.4, 127.4, 127.6, 130.8, 131.5, 134.4, 163.7 ppm.
Typical Synthesis of N-(2-hydroxyethyl)-1,8-naphthalimide in [BMIM][NO_3]: 2-Aminoethanol (150 µL, 2.5 mmol) was added to a stirred suspension of 1,8-naphthalic anhydride (0.459 g, 2.3 mmol) in [BMIM][NO_3] (2.5 mL). The resulting suspension was stirred at 140 °C for 15–20 min. After cooling to 100 °C, the reaction mixture was diluted with EtOH (5 mL) resulting in precipitation of the product. The mixture was then cooled to room temperature with stirring. The precipitated product was collected by filtration, washed with EtOH and dried under vacuum. NMR data and mp as above.
22. http://www.radleys.com/.