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N-Butylpyrrolidinone as a dipolar aprotic solvent for organic synthesis

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James Sherwood,[a] Helen L. Parker,[a] Kristof Moonen,[b] Thomas J. Farmer[a] and Andrew J. Hunt*[a]

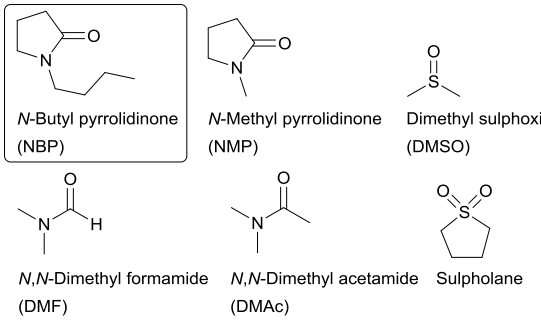
Dipolar aprotic solvents such as *N*-methypyrrolidinone (NMP) are under increasing pressure from environmental regulation. NMP is a known reproductive toxin and has been placed on the EU "Substances of Very High Concern" list. Accordingly there is an urgent need for non-toxic alternatives to the dipolar aprotic solvents. *N*-Butylpyrrolidinone, although structurally similar to NMP, is not mutagenic or reprotoxic, yet retains many of the characteristics of a dipolar aprotic solvent. This work introduces *N*-butylpyrrolidinone as a new solvent for cross-coupling reactions and other syntheses typically requiring a conventional dipolar aprotic solvent.

Introduction

In recent times considerable attention has been drawn to a number of solvents because of their undesirable health, safety, or environmental problems. The motivation to replace these chemicals is driven by legislation in some instances, but more generally it is recognised that the principles of green chemistry can create efficiency savings, as well as reduce the costs associated with hazardous material disposal and alleviate the need for stringent safety precautions.[1] A broad range of different solvents are employed across the various chemical sectors, in both processes and in products. Boiling point, viscosity and numerous other physical properties are all important to the relevance of a solvent in a given application. Of these properties, polarity is the vital attribute of a solvent when it comes to the solubility of components in solution, also controlling the productivity of a reaction through kinetic and thermodynamic phenomena.[2,3] This, in part, is why many solvents are required to satisfy the differing demands of the chemical industries.

As the greatest contribution to the mass of chemicals used in most chemical processes, the solvent is often prioritised for substitution should the need to improve the greenness of a reaction arise. A number of solvents have either been identified or specifically developed as green alternative solvents for this purpose. While some green solvents are recognisable from the catalogue of conventional solvents, many others are neoteric (*i.e.* new or otherwise unconventional) solutions (Fig. 1).[4] The replacement of dipolar aprotic solvents is of urgent need to all chemical sectors given the pressure of impending legislative measures such as the European REACH regulation.[5] The demand for reliable substitutes is high owing to the chronic toxicology of these vital solvents. Recently, a solvent-conserving catalyst has been developed for acid-catalysed reactions, which can aid in reducing the use of dipolar solvents.[6] Despite this there is a pressing need for to address the availability of low toxicity alternative solvents with the correct polarity profile.

Towards this goal of non-toxic dipolar aprotic solvents, *N*-butylpyrrolidinone (NBP) is a promising candidate. It has been identified as being non-reproductively toxic (according to OECD 414 test method), non-mutagenic (OECD 471), and also inherently biodegradable (OECD 302B) (Scheme 1).[7] Despite this, *N*-butylpyrrolidinone has only been used as a reaction medium in a very limited number of academic instances, usually as a co-solvent.[8] It is more acutely toxic (LD_{50} rat oral, 300-2000 mg/kg) than NMP (~4000 mg/kg). This serves as a reminder that the advantages of *N*-butylpyrrolidinone must be counterbalanced by any negative impact in solvent selection. The physical properties of *N*-butylpyrrolidinone are generally similar to other dipolar aprotic solvents. Aside from its lower melting point, Table 1 shows that the physical properties of *N*-butylpyrrolidinone reside within the data ranges established by the conventional dipolar aprotic solvents.



Scheme 1. *N*-Butylpyrrolidinone and other dipolar aprotic solvents.

*[a] *Green Chemistry Centre of Excellence, Department of Chemistry, University of York, YO10 5DD, UK, Email: andrew.hunt@york.ac.uk*
[b] *Eastman Chemical Company, Pantserschipstraat 207 – B-9000, Gent, Belgium.*
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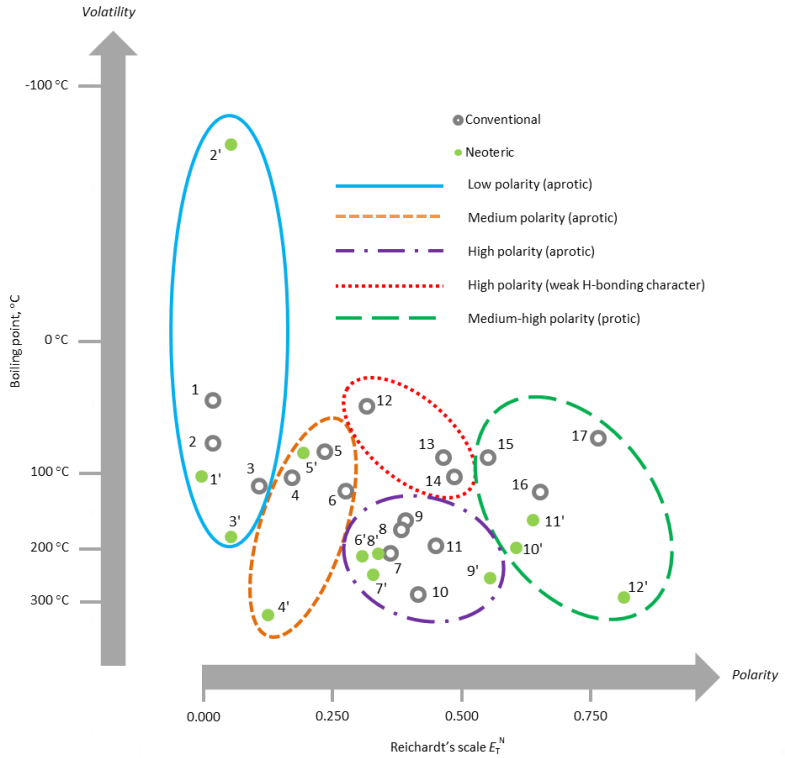


Fig. 1. Conventional and neoteric solvent types arranged by polarity and volatility. Key to conventional solvents: 1, *n*-pentane; 2, *n*-hexane; 3, toluene; 4, 1,4-dioxane; 5, ethyl acetate; 6, methyl isobutyl ketone; 7, NMP; 8, *N*,*N*-dimethyl acetamide (DMAc); 9, *N*,*N*-dimethyl formamide (DMF); 10, sulpholane; 11, dimethyl sulphoxide (DMSO); 12, dichloromethane; 13, acetonitrile; 14, nitromethane; 15, isopropanol; 16, acetic acid; 17, methanol. Key to neoteric solvents: 1', hexamethyldisiloxane; 2', supercritical CO_2; 3', limonene; 4', methyl oleate; 5', 2-methyltetrahydrofuran; 6', γ-valerolactone; 7', N-butylpyrrolidinone; 8', Cyrene; 9', ethylene carbonate; 10', solketal; 11', ethyl lactate; 12', glycerol. Refer to the Electronic Supplementary Information for extra detail and references.

Table 1. Representative physical properties of dipolar aprotic solvents (ref. 9).

Solvent	Melting point /°C	Boiling point /°C	Vapour pressure /Pa	Density /g·mL^{-1}	Viscosity /cP	Flash point /°C
NBP	< -75	241	35 (20 °C)	0.960	4 (25 °C)	108
NMP	-24.4	202	50 (25 °C)	1.03	1.67 (25 °C)	86
DMF	-60.4	153	370 (25 °C)	0.94	0.9 (20 °C)	58
DMAc	-20.1	166	130 (25 °C)	0.94	2.14 (20 °C)	63
DMSO	18.6	189	60 (25 °C)	1.10	2.0 (25 °C)	89
Sulpholane	28.4	287	9.1 (30 °C)	1.26	10.35 (30 °C)	177

The dipolarity (π*) of *N*-butylpyrrolidinone is slightly less than what might be expected of a solvent able to replace any of the traditional dipolar aprotic solvents (Table 2). As seen by comparing NMP and *N*-butylpyrrolidinone, increasing the *N*-alkyl chain length on the pyrrolidinone moiety decreases the dipolarity of the solvent, but through electron donation enhance its hydrogen bond accepting ability (β). As the name suggests, dipolar aprotic solvents are not hydrogen bond donors (α = 0) and for aprotic solvents have reasonably high values on the Reichardt scale of polarity (E_T^N).[10]

Table 2. Solvatochromic polarity data of dipolar aprotic solvents.

Solvent	E_T^N	Ref.	α	β	π*	Ref.
NBP	0.323		0.00	0.92	0.77	
NMP	0.355	[10]	0.00	0.75	0.90	[11]
DMF	0.386	[10]	0.00	0.71	0.88	[11]
DMAc	0.377	[10]	0.00	0.73	0.85	[11]
DMSO	0.444	[10]	0.00	0.74	1.00	[11]
Sulpholane	0.410	[10]	0.00	0.30	0.96	[12]

Differences between the polarity of *N*-butylpyrrolidinone and the other dipolar aprotic solvents mean it cannot be said that *N*-butylpyrrolidinone is automatically a universal replacement for them. Hence the objective of this research was to establish the chemical reactions that could benefit from

the application of *N*-butylpyrrolidinone as the solvent. A detailed assessment of this sort had not been conducted before, thus a series of reactions were performed to compare *N*-butylpyrrolidinone to more conventional dipolar aprotic solvents such as NMP and DMF. *N*-Butylpyrrolidinone was found to be a satisfactory 'drop-in' replacement for dipolar aprotic solvents in varied examples of organic synthesis. It should also be noted that it is also possible to synthesise the *N*-alkylpyrrolidinones from biomass feedstocks, either by feedstock replacement (*e.g.* biogas, bio-butanol) or a new process using glutamic acid to form the intermediate pyrrolidinone.[13]

Results and discussion

In order to ascertain the role of solvents in organic synthesis and gauge their performance relative to one another, free energy relationships correlating the polarity of solvents to the observed reaction kinetics have proven very useful. This graphical interpretation is known as a linear solvation energy relationship (LSER).[14] The reactions chosen for this type of kinetic analysis were a Menschutkin heteroatom alkylation and an example of the Heck cross-coupling reaction. The fluorination of a functionalised pyridine derivative, as previously demonstrated in the literature,[12] was attempted but the progress of the reaction was slow (see Electronic Supplementary Information). The LSER approach, through emphasising the role of the solvent and quantifying each solvent replacement strategy, will exaggerate the differences between solvents. Recording reaction yields or conversions after a set time period is more indicative of the potential of each solvent in preparative scale chemical synthesis. So in addition to the kinetic experiments listed above, the yields of a series of Heck and Suzuki cross-coupling reactions performed in NMP and *N*-butylpyrrolidinone are also reported. Furthermore, a S_N2 reaction and a short screening of 2 different heterocycle syntheses was also undertaken, in which *N*-butylpyrrolidinone promoted reactions are compared to the yields obtained in the traditional solvents.

Menschutkin reaction kinetics

Heteroatom alkylation is the most prevalent reaction practiced in drug discovery.[15] The Menschutkin reaction is a specific version of *N*-alkylation that has found contemporary use in the synthesis of ionic liquids.[16] It also formed the basis of one of the earliest solvent effect studies, where the rate of reaction is strongly dependant on the dipolarity of the solvent.[2] For this reason dipolar aprotic solvents are the favoured reaction medium. Contemporary research has suggested that dimethyl sulphoxide (DMSO) provides the optimum balance between productivity and solvent greenness in the Menschutkin reaction.[16]

The rate of the chosen model Menschutkin reaction between 1-methylimidazole and 1-bromooctane at 323 K was measured in a variety of solvents using ^{1}H-NMR spectroscopy. Then a correlation with solvent polarity was constructed (Fig. 2). The natural logarithms of the experimentally determined rate constants were correlated to the polarity of the solvent. Only π* was found to be statistically significant as an independent variable, and the resulting data fit is satisfactory (see the Electronic Supplementary Information). As expected DMSO provides the greatest rate of reaction in the experimental solvent dataset, with *N*-butylpyrrolidinone offering increased performance over acetonitrile but not DMF and NMP. It may be concluded that, as a dipolar aprotic solvent, *N*-butylpyrrolidinone falls within the expected performance range, but in order to advocate its use ahead of the more established solvents, the favourable environmental health and safety characteristics it possesses must be an integral part of the solvent selection process.

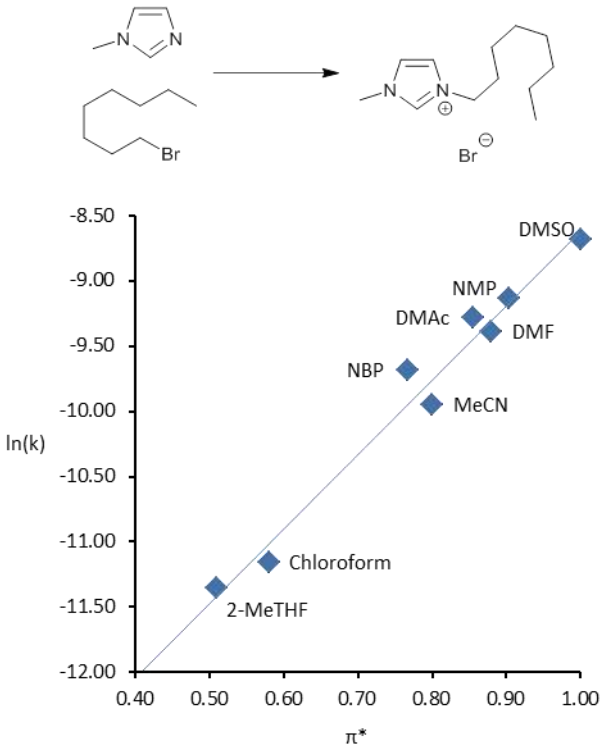


Fig. 2. The LSER describing the rate of a Menschuktin reaction (as drawn).

Benzylation of sodium acetate

The Menschutkin is not typical of S_N2 mechanism reactions because two neutral reactants combine to give an ionic product. It is more routine for an anionic nucleophile to displace the halide (or pseudohalide) leaving group from a molecule. To address nucleophilic substitution more generally, a reaction between potassium acetate and benzyl bromide to give benzyl acetate was studied under different conditions. Firstly, two equivalents of potassium acetate were used at ambient temperature, which allowed for complete conversion to the desired product in DMSO within two hours (Fig. 3). The reaction was slower in NMP and less effective still in *N*-butylpyrrolidinone, but complete within 24 hours. The solubility of the potassium acetate seems to have limited the rate of conversion, as well as the solvent polarity. To overcome this, alternative conditions using only 1.1 equivalents of

potassium acetate, but with the addition of the cation chelator tetramethylethylenediamine (TMEDA) were employed. This resulted in full conversion to benzyl acetate in DMSO, NMP or *N*-butylpyrrolidinone after two hours.

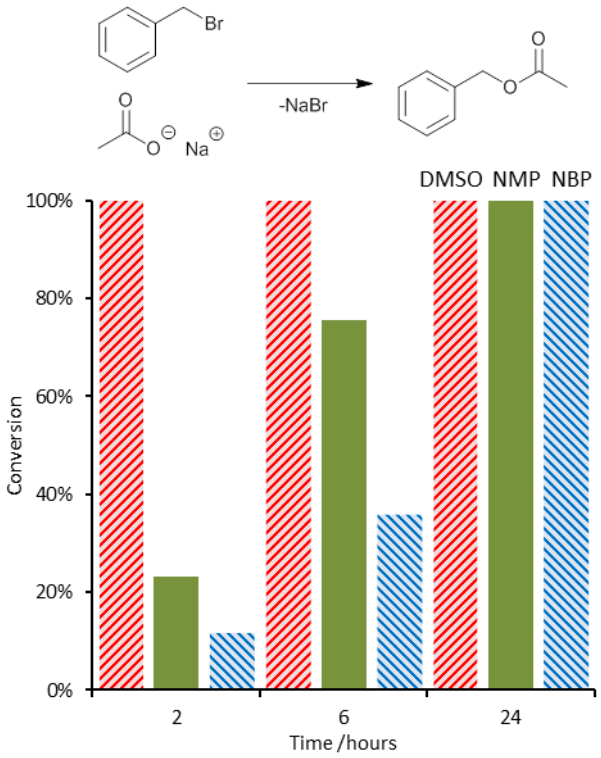


Fig. 3. Ambient temperature conversions of benzyl bromide to benzyl acetate (shown) with 2 equivalents of potassium acetate and no chelating agent.

Cross-coupling studies

Cross-coupling reactions are ubiquitous in the pharmaceutical industry in both medicinal chemistry and drug manufacture.[17,18] Traditionally, cross-coupling reactions such as the Heck reaction are preferentially carried out in highly dipolar aprotic solvents, *e.g.* DMF, NMP DMAc.[18,19] A screening of reaction rates for a model Heck reaction between iodobenzene and methyl acrylate at 373 K was undertaken in the following solvents in order to compare their relative performance: cyclohexanone, *p*-cymene, DMF, DMSO, *N*-butylpyrrolidinone, NMP, and toluene (Fig. 4).

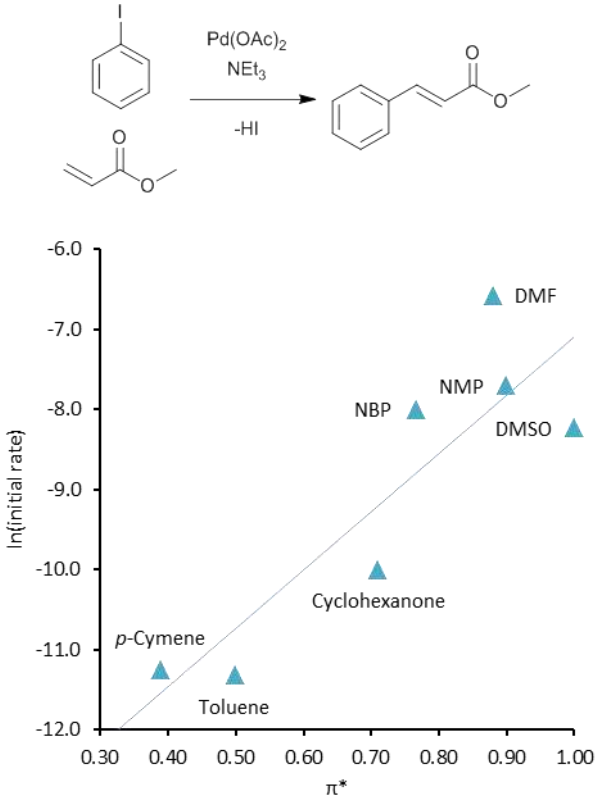
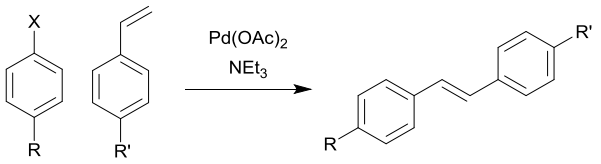


Fig. 4. A model Heck reaction to give methyl cinnamate with the relationship between solvent dipolarity and the natural logarithm of the initial rate of reaction.

The results of the solvent screening indicate the initial rate of reaction to give methyl cinnamate is proportional to the dipolarity of the solvent, again gauged by the Kamlet-Taft solvatochromic π* scale (Fig. 4).[20,21] The complimentary parameter describing hydrogen bond accepting ability (β) was found to be statistically insignificant as was true of earlier case studies. All the solvents are aprotic, with previous experiments indicating that hydrogen bond donating solvents retard the rate of reaction under these conditions.[18] The observed solvent effect is consistent with the common proposal that alkene insertion by palladium is the rate determining step of the Heck reaction with aryl iodides.[22] The polarisation of the alkene results in a separation of charge that is presumably best stabilised in highly dipolar solvents. The rate of reaction in *N*-butylpyrrolidinone is comparable to NMP and DMSO.

To further explore the scope and possible limitations of *N*-butylpyrrolidinone as a solvent in C-C coupling reactions, additional Heck (Table 3) and Suzuki (Table 4) reactions were carried out using a range of different substituted aryl halides and olefins. Reactions were also performed in NMP in order to compare conversions and determine if *N*-butylpyrrolidinone is truly an effective replacement, simultaneously offering an improved toxicological profile. All reactions were carried out for 24 hours to ensure that the reactions were complete. Results indicated that conversion to the product in *N*-butylpyrrolidinone compared well with NMP, generally resulting in comparable or superior yields for all the Heck cross-coupling reactions attempted (Table 3).

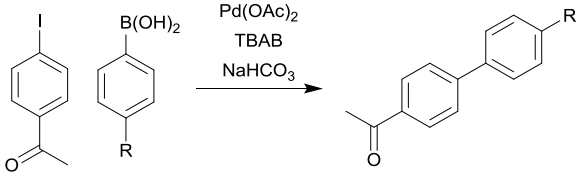
Table 3. A comparion of reaction efficiency for a range of substituted aryl halides in the Heck reaction using *N*-butylpyrrolidinone and NMP as solvents.



	X	R	R′	Conversion* in NMP	Conversion* in NBP
1	I	H	H	91%	92%
2	I	H	Me	96%	94%
3	I	H	OMe	89%	93%
4	I	H	2-Vinylnaphthalene[§]	>99%	>99%
5	I	H	CF_3	94%	90%
6	I	Cl	H	68%	85%
7	I	Cl	Me	>99%	>99%
8	Br	CN	H	85%	87%
9	Br	CN	Me	>99%	>99%

*Conversion calculated from ^{1}H NMR spectra. Reaction conditions are provided in the experimental section. [§]2-Vinylnaphthalene is the olefin reactant.

Table 4. A comparison of reaction efficiency for a range of phenylboronic acids in Suzuki cross-coupling reactions with 4-iodoacetophenone using *N*-butylpyrrolidinone and NMP as solvents.



	R	Conversion* in NMP	Conversion* in NBP
1	H	83%	73%
2	CF_3	76%	72%
3	NO_2	89%	79%
4	OH	87%	77%
5	Me	90%	81%

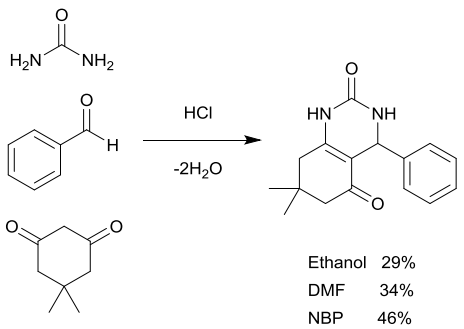
*Conversion calculated from ^{1}H NMR spectra. Reaction conditions are provided in the experimental section.

N-Butylpyrrolidinone was less effective than NMP when applied in the Suzuki cross-coupling reaction (Table 4). It may be that the conditions chosen for the Suzuki reactions (involving the dilution of the solvent with water and the application of tetrabutylammonium bromide (TBAB) as a phase transfer catalyst) are more sensitive to the polarity of the solvent than the examples of the Heck reaction discussed previously in Table 3. *N*-Butylpyrrolidinone is water miscible, but these reactions have not been optimised to specifically favour *N*-butylpyrrolidinone, instead performed according to literature precedent that relies on conventional dipolar aprotic solvents (*e.g.* NMP). The performance of the Suzuki cross-coupling reactions in *N*-butylpyrrolidinone could potentially be improved to meet ordinary expectations with modified conditions, but here the conversions were modest.

Heterocycle syntheses

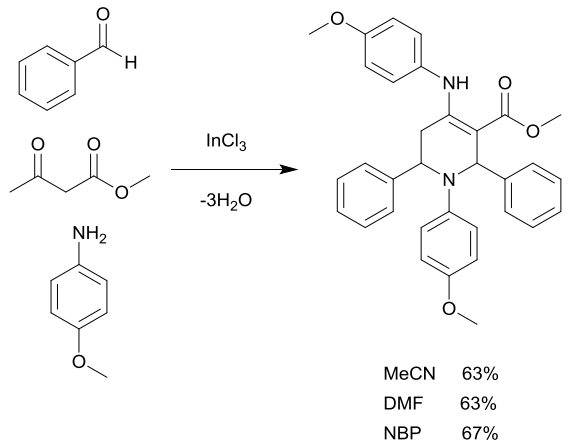
Heterocycle synthesis is a vitally important initial step in the synthesis of many drug precursors, after which functionalisation can provide a diverse range of drug candidates. Often a high polarity solvent is used to conduct a heterocycle synthesis, including multicomponent reactions performed in one pot.[23] A small range of different heterocycles have been synthesised in *N*-butylpyrrolidinone to further demonstrate its potential value as a solvent in the fine chemical and pharmaceutical sector.

The Biginelli reaction yields a dihydropyrimidinone product. Previous work has shown that for Biginelli reactions between urea, an aldehyde, and a cyclic 1,3-dicarbonyl compound (dimedone), solvents with a strong tendancy to accept hydrogen bonds provide the highest yields.[24] For this reason the isolated product yield from the reaction conducted in *N*-butylpyrrolidinone exceeded that when either ethanol (the conventional choice of solvent) or DMF was used as the solvent (Scheme 2).



Scheme 2. An example of a Biginelli reaction with the isolated yields obtained in different solvents indicated.

A modification to the Maitland-Japp reaction produces highly functionalised piperidines.[25] Acetonitrile (MeCN) is routinely used as the solvent in this reaction between a 1,3-dicarbonyl compound, 2 equivalents of an aniline derivative and 2 equivalents of aldehyde. Overnight reactions at the ambient temperature produced yields after recystallisation of 63% in either MeCN or DMF, and 67% in *N*-butylpyrrolidinone (Scheme 3).



Scheme 3. A multicomponent synthesis of piperidines in different solvents and the corresponding yields.

Experimental

Determination of the Kamlet-Taft solvatochromic parameters

The determination of the β Kamlet-Taft solvatochromic parameter was performed in the same manner as originally described with 4-nitroaniline and *N,N*-diethyl-4-nitroaniline.[10] Similarly values of π* were obtained by converting the absorbance maxima wavelengths of *N,N*-diethyl-4-nitroaniline.[20] For α values spectroscopic data from Dimroth-Reichardt's betaine dye was applied after subtracting the contributions of solvent dipolarity.[26] A Jasco V-550 UV-vis. spectrophotometer was used to obtain the required absorbance maxima wavelengths of each dye in solution.

Menschutkin reaction

To a solution of 1-methylimidazole (0.328 g, 4.00 mmol) preheated to 323 K in the chosen solvent (4 mL) was added 1-bromooctane (0.850 g, 4.40 mmol) in a single aliquot. The progression of the reaction as 1-methyl-3-octylimidazolium bromide was formed was monitored by ^{1}H-NMR spectroscopy, ideally until over 50% conversion had been achieved.

Benzyl acetate synthesis (method 1)

Potassium acetate (0.785 g, 8.00 mmol) was added to 20 mL of the chosen solvent and stirred at 450 rpm at the ambient temperature. To the suspension was added benzyl bromide (0.684 g, 4.00 mmol) in a single aliquot. Filtered aliquots were taken at selected intervals in order to monitor the progression of the reaction by ^{1}H-NMR spectroscopy.

Benzyl acetate synthesis (method 2)

Tetramethylethylenediamine (0.511 g, 4.40 mmol) and potassium acetate (0.432 g, 4.40 mmol) was added to 20 mL of the chosen solvent and stirred at 450 rpm at the ambient temperature. Then was added benzyl bromide (0.684 g, 4.00 mmol) in a single aliquot. The reaction was monitored as per method 1 above.

Heck reaction kinetics

Into a 25 mL round bottom flask the following reagents were measured: iodobenzene (30 mmol), methylacrylate (30 mmol), and triethylamine (30 mmol). The chosen solvent (30 mL) was then added and the flask heated with stirring to 373 K. Once the solution was stable at the required temperature, $Pd(OAc)_2$ (0.1 mol% based on iodobenzene concentration) was added. For control experiments no catalyst was added. The reaction was monitored with samples taken at designated intervals. The reaction was allowed to proceed until the yield had reached over 50% conversion. The reaction was monitored by GC-FID using diethyl succinate as a standard. Quantitative analysis of products was conducted using an Agilent 6890 N gas chromatograph with a flame ionisation detector (GC-FID). This was fitted with a DB5HT capillary column (30m x 250 µm x 0.25 µm nominal) at constant pressure of 21.54 psi. The carrier gas used was helium and flow rate was set at 2.2 mL·min^{-1} in constant flow mode. The split ratio used was 40:1. The initial oven temperature was maintained at 323 K for 4 minutes. The temperature was then ramped at a rate of 10 K min^{-1} to 573 K and held for 10 minutes. The injector was set at 563 K and the FID was maintained at 613 K. Peaks were identified by comparison with standard compounds. Quantification of methyl cinnamate yield was determined using peak area comparison between product peak and diethyl succinate standard. From the GC conversions, calculated across a suitable range of reaction times, the rate constant of each reaction could be obtained graphically.

Heck reaction substrate screening

Into a 30 mL Teflon sealed reaction tube the following reagents were measured: aryl halide (15 mmol), olefin (18 mmol), triethylamine (18 mmol). Solvent (6 mL) was then added and the flask heated with stirring to 373 K. Once the flask had heated to the required temperature $Pd(OAc)_2$ (1 mol% based on aryl halide concentration) catalyst was added. Reaction conversions were determined by ^{1}H NMR spectroscopy. ^{1}H NMR spectra were obtained using a JOEL JNM-ECS400 NMR operating at 400 MHz, 1024 scans were taken for each sample.

Suzuki reaction substrate screening

Into a 30 mL Teflon sealed reaction tube the following reagents were measured: aryl halide (2.1 mmol), boronic acid (2.45 mmol), sodium bicarbonate (7 mmol), tetrabutylammonium bromide (4.5 mmol). The chosen solvent (7 mL) and water (3 mL) were then added and the flask heated

with stirring to 323 K. Once heated to the required temperature $Pd(OAc)_2$ (2 mol% based on aryl halide concentration) catalyst was added. Reaction conversions were determined as for the Heck reaction.

Biginelli reaction procedure

Urea (0.300 g, 5.00 mmol), 5,5-dimethyl-1,3-cyclohexanedione (1.05 g, 7.50 mmol) and the chosen solvent (12 mL) were heated to 358 K. Upon reaching thermal equilibrium, benzaldehyde (0.51 mL, 5.00 mmol) and concentrated hydrochloric acid (10 mol%) were added to the mixture. The reaction was stirred at 300 rpm for duration of 24 hours. Upon completion of the reaction, the mixture was allowed to cool to ambient temperature. A small quantity of water was added to ensure complete dissolution of the product. The resultant solid was separated from the reaction mixture by filtration, washed and re-crystallised from ethanol to give 4,6,7,8-tetrahydro-7,7-dimethyl-4-phenyl-2,5(1H,3H)-quinazolinedione as white, needle-like crystals. δ_H(400 MHz; DMSO-d_6) 0.88 (3 H, s, CH_3), 1.00 (3 H, s, CH_3), 2.10 (2 H, q, CH_2), 2.34 (2 H, q, CH_2), 5.14 (1 H, d, CH), 7.34–7.18 (5 H, m, Ar-H), 7.77 (1 H, br s, N-H), 9.47 (1 H, s, N-H). δ_C(100 MHz; DMSO-d_6) 26.9, 28.8, 32.3, 49.8, 52.0, 107.4, 126.3, 127.2, 128.4, 144.7, 152.0, 152.5, 192.2. ESI-MS: *m/z* 271 (M^+ + H).

Piperidine synthesis procedure

To the chosen solvent (1 mL) was added *p*-anisidine (0.517 g, 4.2 mmol), benzaldehyde (0.424 g, 4.0 mmol), methyl acetoacetate (0.232 g, 2.0 mmol), and indium trichloride hydrate (0.159 g, 0.67 mmol). The mixture was stirred at room temperature for 16 hours, then the resultant product filtered. The product was washed with methanol and recrystallized from a mixture of dichloromethane and methanol to give methyl 4-(4-methoxyphenylamino)-1,2,5,6-tetrahydro-1-(4-methoxyphenyl)-2,6-diphenylpyridine-3-carboxylate as a white crystalline solid. δ_H(400 MHz; $CDCl_3$) 2.62 (1 H, dd, CH), 2.78 (1 H, dd, CH), 3.64 (3 H, s, OCH_3), 3.73 (3 H, s, OCH_3), 3.89 (3 H, s, $COOCH_3$), 5.05 (1 H, dd, CH), 6.17 (2 H, d, Ar), 6.32 (1 H, s, CH), 6.43 (2 H, d, Ar), 6.59 (2 H, d, Ar), 6.65 (2 H, d, Ar), 7.22-7.09 (2 H, m, Ar), 7.34-7.22 (8 H, m, Ar), 10.09 (1 H, s, NH). δ_C(100 MHz; $CDCl_3$) 33.7, 51.0, 55.4, 55.7, 58.3, 96.9, 114.0, 114.5, 114.9, 126.3, 126.6, 126.9, 127.2, 128.0, 128.3, 128.7, 130.7, 141.7, 143.3, 144.3, 150.7, 157.1, 158.0, 168.7. ESI-MS. *m/z* 521 (M^+ + H).

Conclusions

It has been demonstrated that *N*-butylpyrrolidinone possesses many of the characteristics of the structurally related solvent NMP or *N*-ethyl pyrrolidinone (NEP) but has the advantage that it is not reprotoxic. *N*-Butylpyrrolidinone is able to deliver comparable yields in Heck cross-coupling reactions and heterocycle syntheses to those obtained in conventional dipolar aprotic solvents. A number of nucleophilic substitution reactions have also been performed, demonstrating the broader capacity of *N*-butylpyrrolidinone as a solvent in organic synthesis. *N*-Butylpyrrolidinone is commercially available in industrial relevant quantities and can now be considered as part of a new set of greener solvent substitutes for conventional dipolar aprotic solvents, complementing the cyclic carbonates,[18] Cyrene,[12] and γ-valerolactone.[27]

Acknowledgements

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