

Evaluation of alternative solvents in common amide coupling reactions: replacement of dichloromethane and *N,N*-dimethylformamide†

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A range of alternative solvents have been evaluated within amidation reactions employing common coupling reagents with a view to identifying suitable replacements for dichloromethane and *N,N*-dimethylformamide.

The amide bond is one of the most fundamental functional group linkages and underpins the connectivity of basic biomolecules (*e.g.*, proteins) as well as being commonly found in many widely used materials (*e.g.*, nylons) and key pharmaceuticals (*e.g.*, penicillin, Lipitor®).^{1,2} In this latter context, amide bond formation is the single most common synthetic transformation used within medicinal chemistry. Indeed, several studies have demonstrated the prevalence of this particular transformation within the pharmaceutical sector: MacDonald's analysis of the GlaxoSmithKline (GSK) Respiratory Centre of Excellence for Drug Discovery revealed that 17% of all reaction types conducted in array (focused library) format were to prepare amide or sulfonamide moieties.³ Similarly, Roughley's analysis of the most common reactions used within synthetic medicinal chemistry research across three of the largest pharmaceutical companies (GSK, AstraZeneca, and Pfizer) indicated that *N*-acylation to prepare amides ranked 1st for frequency of use, accounting for 16% of all reactions performed and with the amide linkage present in 54% of the compound set analysed.⁴

While carboxamide formation is formally a condensation between a suitable carboxylic acid and amine combination that can be achieved simply by heating the requisite components together,⁵ this is typically not an efficient or

particularly useful method due to the formation of an unreactive carboxylate–ammonium salt which commonly leads to poor yields, lengthy reaction times, or substrate compatibility issues.⁶ As such, carboxamide formation is often more conveniently achieved through application of a suitable coupling agent.⁷ Over the years, amide bond coupling reagents have been the subject of some considerable development to the stage that a bank of these reagents are available for deployment and guides have been devised to assist the practitioner in selecting the most effective reagent for a desired amidation.⁸

Throughout this area, however, the most widespread solvents employed are those with major regulatory issues such as chlorinated (dichloromethane, 1,2-dichloroethane) or *N,N*-dimethylformamide (DMF). For example, a survey of amidation reactions using SciFinder revealed that 83% of approximately 680 000 amidation reactions employed either CH₂Cl₂ (36%) or DMF (47%) as the reaction media.⁹ By contrast, the emerging green solvent 2-methyltetrahydrofuran accounted for only 0.04% of this reaction set.⁹ Despite their utility, CH₂Cl₂ and DMF are clearly not compatible with the current drive towards more sustainable and environmentally cognisant medicinal chemistry processes.¹⁰

As part of a programme focused on enabling sustainable medicinal chemistry practices, we have been interested in addressing solvent selection within both reaction and purification scenarios.¹¹ Herein, we describe our evaluation of a selection of alternative solvents for use within amidation reactions using common amide coupling agents with a view to identifying suitable replacements for CH₂Cl₂ and DMF.

Results and discussion

Methods

For our study, we elected to use five of the most common amide coupling reagents or reagent combinations: (1-cyano-2-ethoxy-2-oxoethylideneaminoxy)dimethylamino-morpholino-carbenium hexafluorophosphate (COMU),¹² *N,N'*-diisopropylcarbo-

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diimide/hydroxybenzotriazole (DIC/HOBt),¹³ *N*-[(dimethylamino)-1*H*-1,2,3-triazolo-[4,5-*b*]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide (HATU),¹⁴ (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP),¹⁵ and *n*-propylphosphonic anhydride (T3P®)¹⁶ (Fig. 1). In addition, we aimed to evaluate these reagents within the amidation reactions of representative examples of both aryl and alkyl acids and amines in order to probe alkyl-alkyl, aryl-aryl, and alkyl-aryl couplings (Fig. 1). In terms of solvent selection, to compare directly with CH₂Cl₂ and DMF, we selected emerging or existing solvents including *tert*-butyl methyl ether (TBME), cyclopentylmethyl ether (CPME), dimethylcarbonate (DMC), ethyl acetate (EtOAc), iso-propyl alcohol (IPA), and 2-methyltetrahydrofuran (2-MeTHF) (Fig. 1).¹⁷ Other potential alternative solvents such as MeOH, EtOH, and acetone were discounted based on unfavourable potential side reactions (esterification and condensation

pathways). Overall, we elected to evaluate 160 different sets of reaction conditions in this initial stage of our survey.

To ascertain the reaction performance of the alternative solvents, we analysed each reaction by HPLC at a range of time points (0 h, 1 h, 2 h, 3 h, 4 h, 5 h, 6 h, 8 h, and 24 h) to give a conversion curve, which could be directly compared across the

Amide Coupling Reagents	Solvent Selection	
COMU	<i>tert</i> -Butyl methyl ether (TBME)	<i>N,N</i> -Dimethylformamide (DMF)
DIC/HOBt	Cyclopentyl methyl ether (CPME)	Ethyl acetate (EtOAc)
HATU	Dichloromethane (CH ₂ Cl ₂)	<i>iso</i> -Propyl alcohol (IPA)
PyBOP	Dimethylcarbonate (DMC)	2-Methyl tetrahydrofuran (2-MeTHF)
T3P		

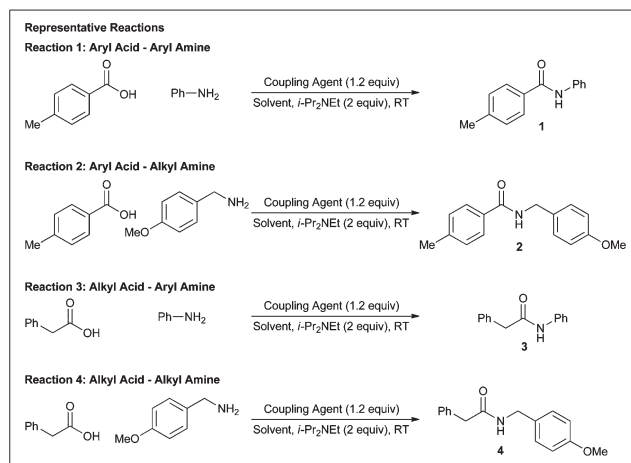


Fig. 1 Coupling agents, solvents, and representative reactions for the amidation survey.†

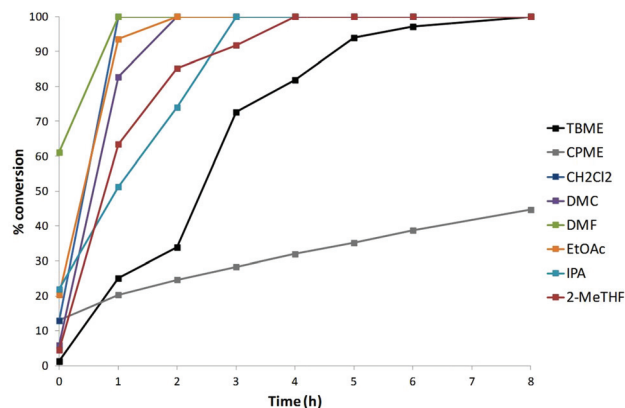


Fig. 2 Representative example of conversion data: amidation Reaction 3 using HATU with the range of solvents.†

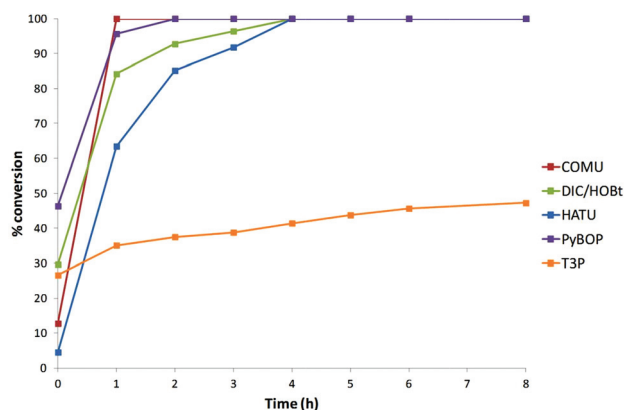


Fig. 3 Representative example of conversion data: amidation Reaction 3 with the range of coupling agents in 2-MeTHF.†

Table 1 Illustrative representation of the amidation dataset^a

Solvent	Amide Coupling Type																			
	Aryl Acid – Aryl Amine					Aryl Acid – Alkyl Amine					Alkyl Acid – Aryl Amine					Alkyl Acid – Alkyl Amine				
	HATU	COMU	DIC HOBt	PyBOP	T3P	HATU	COMU	DIC HOBt	PyBOP	T3P	HATU	COMU	DIC HOBt	PyBOP	T3P	HATU	COMU	DIC HOBt	PyBOP	T3P
TBME	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	**	**	**	**	*
CPME	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	**	**	**	**	**
CH ₂ Cl ₂	**	*	*	*	*	*	**	*	*	*	**	**	*	*	*	*	**	**	**	**
DMC	*	*	*	*	**	**	**	**	**	**	*	*	*	*	*	**	**	*	**	*
DMF	**	**	**	*	*	*	*	**	**	**	**	**	*	*	*	**	**	**	**	**
EtOAc	*	*	*	*	**	**	**	**	**	**	*	*	*	*	*	**	**	**	**	**
IPA	*	*	*	*	*	**	**	*	**	*	*	*	*	*	*	**	**	**	**	*
2-MeTHF	*	*	*	*	*	*	*	*	*	*	*	**	*	*	*	*	**	*	*	**

^a Key: Red = <50% conv., orange = 50–70% conv., green = >70% conv.; * Indicates 100% conv. within 4 h. ** Indicates 100% conv. within 1 h.



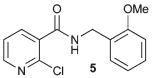
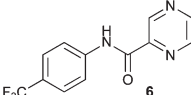
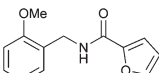
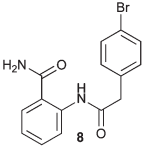
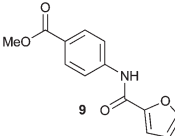
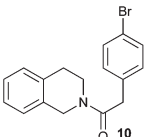
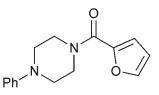
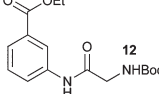
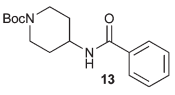
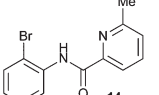
solvent selection. Reactions and aliquots were repeated and analysed up to a maximum of four times to ensure reliability.†

Analysis

An illustrative example chart of conversion *vs.* time for Reaction 3 using HATU is shown in Fig. 2. The data indicated that this amidation proceeded effectively in most solvents and

was generally complete after 4 h with the exception of TBME (8 h) and CPME (24 h – data point not shown). An alternative view of a section of the generated data is obtained from analysis of coupling agents for a particular reaction in a given solvent. For example, Fig. 3 displays the conversion *vs.* time data for Reaction 3 in 2-MeTHF using the five coupling agents.†

Table 2 Assessment of promising solvents in a range of amidations using COMU as the preferred coupling agent^a

Entry	Product	Completion time ^b				
		CH ₂ Cl ₂	DMF	DMC	EtOAc	2-MeTHF
1		4 h	4 h	4 h	4 h	4 h
2		4 h	4 h	4 h	4 h	4 h
3		4 h	4 h	4 h	4 h	4 h
4		24 h	24 h	4 h	4 h	4 h
5		4 h	5 min ^c	24 h	4 h	48 h
6		24 h	24 h	4 h	4 h	4 h
7		5 min ^c	4 h	4 h	5 min ^c	5 min ^c
8		24 h	24 h	4 h	4 h	4 h
9		4 h	5 min ^c	4 h	4 h	4 h
10		4 h	4 h	4 h	24 h	4 h

^a Reaction conditions: acid (1 equiv., 0.2 mmol), amine (1.2 equiv., 0.24 mmol), *i*-Pr₂NEt (2 equiv., 0.4 mmol), COMU (1.5 equiv., 0.3 mmol), solvent (1 mL, 0.2 M), RT. ^b Determined by HPLC analysis. See ESI. ^c Taken at 0 h time point, represents first data point sampled.



From consideration of the overall data set (see ESI[†]), a series of general observations could be made. Firstly, unsurprisingly, aryl–aryl couplings (Reaction 1) tended to be the slowest processes in general while alkyl–alkyl couplings (Reaction 4) were faster overall. Most reactions (81% of the dataset) proceeded to 100% conversion, 74% were complete within 4 h, and 36% were complete within 1 h. In terms of general trends observed for the array of solvents: (i) TBME was generally good for aryl–aryl (Reaction 1) and alkyl–alkyl (Reaction 4) couplings and poor for aryl–alkyl (Reaction 2) and alkyl–aryl (Reaction 3) couplings. (ii) CPME was generally poor across the spectrum of reaction conditions examined with the exception of the more reactive alkyl–alkyl coupling (Reaction 4), Reaction 1 using HATU, PyBOP, and T3P, and Reaction 2 using T3P. (iii) As expected, CH₂Cl₂ and DMF were generally very good for all reactions. (iv) Pleasingly, DMC, EtOAc, and 2-MeTHF were found to be generally very good for all reactions. (v) Somewhat surprisingly, IPA performed very well with only a few exceptions (particularly for Reaction 3). An additional observation relating to TBME and CPME is that reactions tended to become heterogeneous as time progressed. This may help to explain why these reactions were generally less successful than the equivalent reactions in the other solvents. Lastly, all coupling agents were effective in each class of reaction (depending on solvent as discussed above) with the exception of T3P for alkyl acid–aryl amine couplings (Reaction 3) which were generally very poor. An illustrative summary of the overall analysis is provided in Table 1.

Based on all of this, it was evident that DMC, EtOAc, and 2-MeTHF were the alternative solvents which offered the greatest potential as replacements for CH₂Cl₂/DMF. Additionally, COMU has emerged as an effective and greener amide coupling agent which operated efficiently within the benchmark reaction survey and, indeed, in several cases more effectively than the ‘gold standard’²ⁿ reagent HATU. As such, we decided to further evaluate DMC, EtOAc, and 2-MeTHF as the reaction solvent alongside CH₂Cl₂ and DMF for comparison utilising COMU as the coupling agent over a broader range of substrates possessing increased functionality (Table 2). Based on observations from the screening process that reactions using COMU in DMC, EtOAc, and 2-MeTHF were generally complete within 4 h, the reactions in Table 2 were analysed at 0 h (effectively within 5 min), 4 h and 24 h. In addition to increased functionality, the acids and amines were selected on the basis that they would deliver amide products that had a physicochemical profile that was consistent with being lead-like (H-Bond Acceptors, 2–7; H-Bond Donors, 0–2; Rotatable Bonds, 3–10; Polar Surface Area, 20–93 Å²; Molecular Weight, 231–332; Xlog P, 0–2.4).¹⁸

As can be seen from Table 2, the amidation reactions were generally complete within the first four hours and comparable to CH₂Cl₂ and DMF in the majority of reactions. Indeed, there were very few cases where CH₂Cl₂ or DMF were shown to outperform the alternative solvents over the substrate range evaluated under these reaction conditions. Overall, these results suggest that DMC, EtOAc, and 2-MeTHF would be effective

replacements for CH₂Cl₂ and DMF for similar amidation processes. In addition, and with specific regard to DMF, an additional practical value of employing DMC, EtOAc, or 2-MeTHF as alternatives is that they would simplify the work up procedure involved prior to any purification as both the boiling points and the water miscibility of these solvents are considerably lower than that of DMF,¹⁷ leading to more effective aqueous work up and concentration processes, where appropriate.

Conclusions

In summary, we have evaluated several alternative solvents as potential replacements for CH₂Cl₂ and DMF as the medium for four benchmark amide bond forming reactions using common amide coupling reagents or reagent combinations. These studies revealed that CH₂Cl₂ and DMF could potentially be readily replaced with more environmentally acceptable and sustainable alternatives. We subsequently applied three of these solvents in a range of amidation reactions using a variety of carboxylic acids and amines with functionality frequently encountered within Medicinal Chemistry programmes, employing COMU as the preferred coupling agent. This assessment demonstrated that the general rates of reaction using DMC, EtOAc, and 2-MeTHF were broadly comparable to those observed using CH₂Cl₂ or DMF and delivered equally high levels of conversion to product. Overall, we believe that DMC, EtOAc, and 2-MeTHF would be practical alternatives to conventionally-used media for routine amide coupling processes and would be highly beneficial for more environmentally benign synthesis programmes in both academia and industry.

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