Tetrahedron Letters 58 (2017) 4391–4394

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A comparative study of amide-bond forming reagents in aqueous media – Substrate scope and reagent compatibility

Matthew Badland [a], Robert Crook [a], Bastien Delayre [b], Steven J. Fussell [a,*], Iain Gladwell [a],
Michael Hawksworth [a], Roger M. Howard [c], Robert Walton [a], Gerald A. Weisenburger [c]

[a] *Pfizer Worldwide Research and Development, Discovery Park, Sandwich, Kent CT13 9NJ, United Kingdom*
[b] *CPE Lyon, 43 Bd du 11 Novembre 1918, F-69100 Villeurbanne, France*
[c] *Pfizer Worldwide Research and Development, Eastern Point Road, Groton, CT 06340, United States*

ARTICLE INFO

Article history:
Received 26 August 2017
Revised 3 October 2017
Accepted 5 October 2017
Available online 7 October 2017

Keywords:
Amide-bond forming
Condensation in water
Coupling reagents

ABSTRACT

A survey of amidation reagents demonstrating DIC-HOPO, DMT-MM, COMU-collidine, TPTU-NMI, EEDQ, CDI and EDC-Oxyma to be effective for the coupling of carboxylic acids with amines in the presence of water and the absence of problematic dipolar aprotic solvents is reported. DMT-MM was shown to provide the best yields for the coupling of a secondary amine, TPTU-NMI and COMU-collidine for aniline, whilst the combination of DIC with HOPO afforded the broadest substrate scope and the highest yields for a sterically demanding carboxylic acid.

The amide functionality is an important component of many drug molecules. A recent survey showed that amidation featured in approximately 50% of all *Journal of Medicinal Chemistry* manuscripts examined, making it the most frequently used synthetic transformation, and importantly with 30% as the final bond forming step.[1] Amide bonds are typically synthesised by reactions of carboxylic acids and amines with the loss of water, in most cases aided by a coupling reagent. A plethora of coupling reagents are commercially available and have been widely used in large-scale manufacture of drug candidates.[2,3] Regrettably, undesirable dipolar aprotic solvents (particularly the reprotoxic solvents dimethylacetamide (DMAC), dimethylformamide (DMF) and *N*-methyl pyrrolidone (NMP) are commonly used[2b,3] due to the poor organic solubility of carboxylic acids, carboxylate salts (including amine/carboxylic acid salt pairs) and zwitterionic substrates. A number of these solvents are deemed substances of high concern and are subject to considerable attention under European REACh regulation.[4] Given the importance of amidation reactions, REACh-unencumbered solvent systems would be highly desirable in designing new scaleable chemical processes.

It is commonly known that carboxylic acids, carboxylate salts and α-amino acids can be readily solubilized in aqueous solvent systems thus providing a potential alternative to dipolar aprotic solvents. However, for the amide coupling to succeed the rate of aminolysis must be significantly greater than the rate of hydrolysis of the activated carboxylic acid intermediate(s) and the coupling reagent itself. A variety of reagents have been reported to provide such conditions- most notably EDC,[5] DPTF,[6] DMT-MM,[7] CDI,[8] COMU[9] and *N*-carboxyanhydrides (NCAs).[10] Herein we describe our efforts to investigate and understand the performance of new and existing water-compatible amide coupling systems.

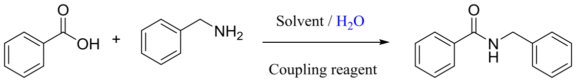
The study was initiated by screening 48 different coupling conditions for the amidation of benzoic acid with benzylamine in the presence of water (Fig. 1). The reaction were initially carried out using NMP as an organic co-solvent to mitigate any solubility issues and was executed by simultaneous addition of the carboxylic acid and amine to the amidation reagent in solution. A range of coupling reagents were shown to afford moderate to high *in situ* yields. Lead reagents selected for further study included a variety of carbodiimides (Table 1, entries 2–6, 8, 9, 11), triazines (Entries 14, 15, 20–22), quinoline based reagents (Entries 23, 24), COMU (Entry 25), TPTU (Entry 41), pivalic anhydride (Entry 42) and CDI (Entry 45).

Using the lead reagents described above, each system was optimized for solvent, additive, order of addition and reaction time in the model reaction (Fig. 1). Problematic dipolar aprotic co-solvents were omitted at this stage in favor of non-reprotoxic alternatives. *N*,*N*′-Diisopropylcarbodiimide (DIC) in combination with HOPO as an additive, was shown to be of particular interest affording the highest *in situ* yields of product 3 (Table 2, entry 1). An EDC-Oxyma cocktail[5b] also gave promising results, as did DMT-MM·BF_4 which

---

[*] Corresponding author.
E-mail address: Steven.Fussell@pfizer.com (S.J. Fussell).

https://doi.org/10.1016/j.tetlet.2017.10.014
0040-4039/



1 2 3

Fig. 1. Model reaction for the screening experiments.

Table 2
Optimized yields for the coupling of benzoic acid with benzylamine in MeCN/Water. See ESI for conditions.

Entry	Reagent	Additive	Yield (%)[a]
1	DIC	HOPO	93
2	DIC	Oxyma	80
3	DIC	HOBt·H_2O	81
4	EDC	Oxyma	82
5	DMT-MM·BF_4		90
6	DMT-MM·Cl		58
7	COMU	Collidine	87
8	TPTU	NMI	90
9	EEDQ		63[b]
10	IIDQ		79[b]
11	Pivalic anhydride		58[c]
12	CDI		85[c]

[a] *In situ* yield by comparison to 1,3-benzodoxole as an internal standard.
[b] Addition of 4M HCl (0.1 eq.) in dioxane, 72 h reaction time.
[c] Sequential activation of the carboxylic acid in acetonitrile followed by addition of the amine coupling partner as an aqueous solution.

significantly outperformed the corresponding chloro analogue (Entries 4–6). Improvement of the *in situ* yields for the TPTU and COMU systems required the addition of an organic base. *N*-Methylimidazole (NMI) in combination with TPTU (Entry 8) and collidine with COMU (Entry 7) proved to be the two best combinations of those tested, mirroring the system reported by Lipshutz and co-workers who employed a surfactant with a COMU and collidine reagent cocktail.[9] In contrast, optimization of the quinoline-based coupling reagents indicated the requirement for sub-stoichiometric amounts of hydrochloric acid and longer reaction times (Entries 9 and 10). In the case of CDI and pivalic anhydride, a yield enhancement was achieved by sequential activation of benzoic acid in acetonitrile followed by the addition of benzylamine as an aqueous solution (Entries 11 and 12). Additional co-solvent screening demonstrated that NMP could be readily replaced by non-reprotoxic water-miscible alternatives such as acetonitrile and tetrahydrofuran (see ESI, Section 3.1).

Following these initial studies, the substrate scope of each of the preferred amidation conditions was investigated (Table 3). The results, as expected, confirmed that the performance of each coupling reagent is substrate-dependent, underlining the importance of reagent screening when developing an amide bond forming process. COMU-collidine demonstrated one of the broadest substrate scopes, affording moderate to high yields for the coupling of both benzoic acid and 3-phenylpropanoic acid with primary and secondary amines including aniline (Table 3, entries 1–4 and 9–12). Similarly, TPTU-NMI showed broad scope and coupled aniline effectively. However, both COMU-collidine and TPTU-NMI were unable to couple the sterically hindered 2,6-dimethylbenzoic acid resulting in little or no product being formed with either amine partner tested (Entries 13 and 14). DMT-MM performed well for the coupling of dibenzylamine, generally outperforming all other coupling reagents for this amine (Entries 4, 8 and 12), yet it did not readily accept aniline or 2,6-dimethylbenzoic acid coupling partners. EEDQ and EDC-Oxyma achieved modest yields with no clear trends for substrate scope shown. The traditional reagent, CDI, was effective for the coupling of aliphatic primary amines with sterically unhindered acids (Entries 2, 3, 6, 7, 10 and 11) but only moderately so for aniline and poorly so for dibenzylamine (Entries 1, 4, 5, 8, 9 and 12). In contrast to all other reagents, the combination of DIC-HOPO was shown to perform well with all carboxylic acid and amine partners tested. Pleasingly, under forcing conditions (70 °C 2 d), DIC-HOPO even accepted the sterically demanding 2,6-dimethylbenzoic acid with both benzylamine and pyridin-2-ylmethanamine (Entries 13 and 14). However, dimethylbenzoic acid was not as well coupled to aniline and dibenzylamine, giving negligible conversions at 20 °C and thus was not optimized (results not presented).

Reaction profiling of the amidation of 2,6-dimethylbenzoic acid with benzylamine showed that the addition of HOPO with DIC

Table 1
Coupling reagent (1.0 eq.) screen for the amidation of benzoic acid with benzylamine (1.0 eq.) in NMP (21 mL/g)/water (9 mL/g) at 20 °C.

Entry	Type	Reagent	Yield (%)[a]	Entry	Type	Reagent	Yield (%)[a]
1	Carbodiimide	DCC	13	25	Uronium/Aminium	COMU	40
2		DCC-HOBt·H_2O	65	26		HOTU	32
3		DCC-Oxyma	63	27		HATU	52
4		DIC	65	28		HBTU	52
5		DIC-HOBt·H_2O	86	29		HCTU	50
6		DIC-Oxyma	81	30		HATU-HOBt·H_2O	49
7		EDC	4	31		HBTU-HOBt·H_2O	50
8		EDC-HOBt·H_2O	82	32		HCTU-HOBt·H_2O	46
9		EDC-Oxyma	83	33		HBTU-Oxyma	46
10		EDC methiodide	3	34		TPTU	49
11		EDC methiodide-HOBt·H_2O	79	35		HSTU	11
12		CMC	1	36		TSTU	12
13		EDC·HCl	42	37		TOTU	35
14	Triazine	DMT-MM·Cl	59	38	Phosphonium	PyAOP	32
15		DMT-MM·BF_4	94	39		PyBrOP	12
16		Cyanuric chloride	15	40	Imidazolium	CIP	23
17		Cyanuric chloride-QD[b]	30	41		DMC	20
18		DCMT	13	42	Miscellaneous	Pivalic anhydride	59
19		DCMT-QD[b]	41	43		Benzyl chloroformate	28
20		CDMT	62	44		TFFH	20
21		CDMT-QD[b]	83	45		CDI	36
22		CDMT-DABCO	68	46		DPP	0
23	Quinoline	EEDQ	54	47		DTPC	2
24		IIDQ	42	48		TODT	25

[a] *In-situ* yield by HPLC analysis with 1,3-benzodoxole as an internal standard.
[b] Quinuclidine abbreviated to QD.