Pergamon

Tetrahedron Letters 42 (2001) 6703–6705

TETRAHEDRON LETTERS

An efficient one-pot, purification-free, preparation of amides using polymer-supported reagents

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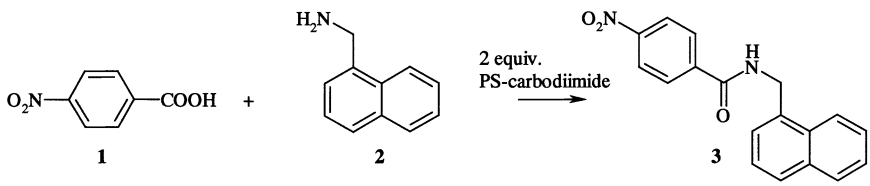
Received 5 April 2001; accepted 27 July 2001

Abstract—A new one-pot method for amide preparation using polymer-supported carbodiimide is reported. It incorporated the use of HOBT to improve the reactivity of the supported reagent and expand the scope of this reaction. HOBT could then be subsequently easily removed from the medium with a supported carbonate base.

In the course of our lead optimization programs we were looking for a very simple and universal method to produce small amides libraries from carboxylic acids. We turned our attention toward the use of supported reagents as a way to reduce lengthy and tedious purification steps.[1] The simplest method to prepare a library of amides is to react amines with excess of acid halides to ensure completion of the reaction, then removal of

Table 1. Optimization of the conditions



Entry	**1** (equiv.)	HOBT (equiv.)	PS-base[a] (3 equiv./equiv. HOBT)	Results (%)		
				Conversion	Purity[b]	HOBT scavenging[c]
1	1	0	–	26	24	–
2	1	0.5	PS-trisamine	66	61	70
3	1	1	PS-trisamine	77	73	68
4	1	1.5	PS-trisamine	96	95	66
5	1.2	0	–	26	25	–
6	1.2	0.5	PS-DMAP	87	81	27
7	1.2	1	PS-DMAP	96	89	37
8	1.2	1.5	PS-DMAP	100	96	48
9	1.5	0	–	27	26	–
10	1.5	0.5	MP-carbonate	89	85	100
11	1.5	1	MP-carbonate	92	86	99
12	1.5	1.5	MP-carbonate	100	96	100

[a] The reagents are available from Argonaut Technologies Inc. Loading of the resins: PS-trisamine 3–4 mmol/g; PS-DMAP 1.1–1.8 mmol/g; MP-carbonate 2.8–3.5 mmol/g.

[b] The purity of the reaction was measured at 220 nm, on a C18 symmetry column (4.6×50 mm; 5 μm), using a linear gradient from 100% water (0.05% TFA) to 100% CH_3CN (0.05% TFA) in 8 min (flow rate: 2.5 ml/min).

[c] The efficiency of HOBT scavenging was assessed at 304 nm, using the formed amide as an internal standard.

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0040-4039/01/$ - see front matter
PII: S0040-4039(01)01387-9

the excess by addition of a supported electrophile (usually an amine).[2] Both reaction and scavenging steps are performed in the same reactor. The procedure is therefore reduced to two sequences of addition, one filtration and finally one evaporation. We were looking for a comparable method that would enable the direct use of carboxylic acids, which are more available commercially and more represented in our, in house, intermediates library. Several two-step processes have already been reported that incorporate the isolation of a supported activated form of the carboxylic acid.[2] We also found several reports of a one-step process using only supported carbodiimides.[3] Unfortunately, in our hands, this latter procedure appeared to give unsatisfactory results in terms of range of application. We thought that this could be due to a certain lack of reactivity of the reagent and that the concomitant use of HOBT would help to expand the scope of the reaction. However, the use of HOBT as a soluble reagent will introduce the problem of its separation from the final product at the end of the reaction. Since a purification step is unacceptable in the preparation of libraries, we decided to use the weak acidity of HOBT to trap it with a supported base.[4] These modifications should extend the scope of this reaction to a large number of carboxylic acids without the limitation of a time consuming purification step.

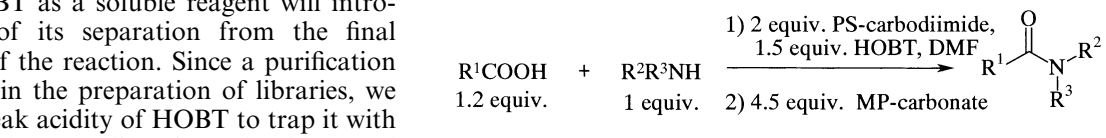
The commercially available PS-carbodiimide[5] was chosen for this study. All reactions were performed in DMF in order to reduce solubility problems.[6] In some instances, when solubility was not a limitation, DMF was successfully replaced with the more volatile CH_2Cl_2, provided that it did not contain any traces of methanol. For the initial set up of the optimum conditions, carboxylic acid **1** and amine **2** were chosen because they represented the average reactivity of our substrate pool and they both incorporated a chromophore allowing HPLC monitoring of the reaction.

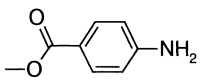
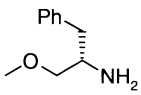
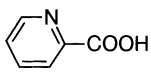
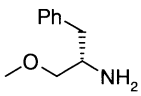
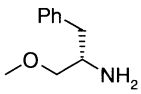
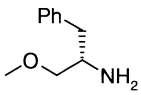
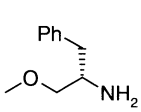
The experimental procedure was simple. Carboxylic acid **1** was dissolved in DMF (2 ml) and mixed with 2 equiv. of PS-carbodiimide and HOBT. After 15 min of stirring the amine was added. The progress of the reaction was monitored every 2 h by HPLC. Finally, in all reactors containing HOBT, a supported base was added at the end of the reaction to scavenge HOBT. The results are reported in Table 1. The presence of HOBT did not have a marked effect on the transformation kinetics, and all reactions were at a standstill after 4 h. However, it was found to have a dramatic effect on the efficiency of the synthesis, and the best conditions were obtained with 1.5 equiv. of HOBT. Even though HOBT is regenerated during the course of the reaction, a catalytic amount of this reagent does not allow completion of the reaction. In the scavenging step, the supported carbonate was found clearly superior to the two other bases. Indeed, after 3 h of stirring, only MP-carbonate was able to completely trap HOBT (entries 10–12). The conditions described in entry 12 were selected for the remaining of the study, using only 1.2 equiv. of carboxylic acid.

In Table 2, entries 1 through 8 show the high efficiency of this process using commercially available amines and acids (used as received). The reactions proceeded well with all aliphatic amines, even with the most hindered *tert*-butylamine. Aromatic amines tended also to give good results, with the exception of the most deactivated one (entry 6). Entries 9 through 11 were performed to show that this procedure could also be applied to small peptide syntheses. In this set of conditions, the fmoc protecting group was stable, and no racemization could be detected by chiral HPLC analysis[8] (entries 10 and 11) with the two Boc-protected phenylalanines.

In conclusion, we have developed a clean and easy one-pot procedure for the synthesis of amides from carboxylic acids, that avoids the time-consuming purifi-

Table 2. Scope of the reaction[7]



Entry	R^1COOH	R^2R^3NH	Yield (%)	Purity (%)[a]
1	**1**	Piperidine	88	93
2	**1**	$nPrNH_2$	99	91
3	**1**	*tert*-$BuNH_2$	93	90
4	**1**	$PhNH_2$	81	88
5	**1**	4-Methoxy-aniline	83	99
6	**1**		0	–
7	PhCOOH		98	95
8			98	81
9	Fmoc-Phe-OH (L)		88	85
10	Boc-Phe-OH (L)		96	92
11	Boc-Phe-OH (D)		100	94

[a] The purity of the reaction was measured at 220 nm, on a C18 symmetry column (4.6×50 mm; 5 μm), using a linear gradient from 100% water (0.05% TFA) to 100% CH_3CN (0.05% TFA) in 8 min (flow rate: 2.5 ml/min).

cation step. Today it is regularly used in our laboratory for the preparation of small size libraries and has proven to be as efficient as the homogeneous conditions.

Acknowledgements

Marc Lannuzel wishes to thank Dr. C. Périgaud and Dr. G. Gosselin for their continuous support on his work.

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4. Flynn, D. L.; Devraj, R. V.; Naing, W.; Parlow, J. J. *Med. Chem. Res.* **1998**, *8*, 219–243.
5. PS-carbodiimide is available from Argonaut Technologies Inc. (0.9–1.4 mmol/g).
6. In the first attempts, a major impurity was observed and was identified as the dimethylamino derivative arising from the degradation of DMF. This problem was easily overcome with the use of fresh DMF.
7. Structure elucidation of entry 8 example: ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.89 (d, 2H, $J=6.8$ Hz); 3.28 (s, 3H); 3.39 (dd, 1H, $J_1=9.6$ Hz, $J_2=5.2$ Hz); 3.45 (dd, 1H, $J_1=9.6$ Hz, $J_2=6.0$ Hz); 4.30–4.40 (m, 1H); 7.10–7.30 (m, 5H); 7.60 (dd, 1H, $J_1=4.8$ Hz, $J_2=9.0$Hz); 7.95–8.00 (m, 2H); 8.55 (d, 1H, $J=9.0$ Hz); 8.64 (d, 1H, $J=4.5$ Hz, NH); MS (ESI): 271 (MH+); $[\alpha]_D^{24}=-60.6°$ (MeOH; *c*, 0.5).
8. Chiral HPLC conditions: ChiralPak AD column (250×4.6 mm I.D.), *n*-hexane/ethanol 80/20, 220 nm, 1 ml/min.