SHORT PAPER

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Solid phase synthesis of amides using Mukaiyama's reagent

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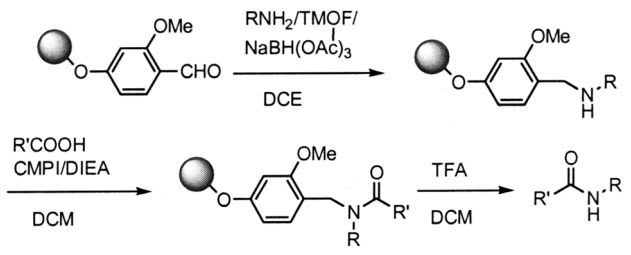
A new solid-phase synthetic method using Mukaiyama's reagent under mild conditions is reported to prepare amides in high purity without purification after cleavage from the resins.

Keywords: solid phase synthesis, formyl resin, Mukaiyama's reagent, coupling reaction, amide formation

Solid phase synthesis has emerged as a powerful approach for combinatorial chemistry for the development and optimisation of a wide variety of compound libraries, especially for peptides[1] and now its use has been expanded to preparation of small molecule libraries.[2] The amide formation reaction is one of the fundamental reactions of solid phase synthesis. Among the commonly available reagents useful for the formation of amides from acids and amines on solid support are dicyclohexylcarbodiimide (DCC),[3] diisopropylcarbodiimide (DIC),[4] benzatriazole - 1 - yloxy - tris - (dimethylamino)-phosphoniumhexafluorophosphate (BOP),[5] bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBroP),[6] 2-(1*H*-benzotriazole-1-yl)-1,1,3,3,-tetramethyluronium tetrafluoroborate (HBTU),[7] and more recently, *N*-[(dimethylamino)-1H-1,2,3-triazolo[4,5-*b*]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide (HATU),[8] *etc*. All these reagents were developed mainly for peptide chemistry and have successfully been used for coupling amino acids. In order to develop more diverse small molecule libraries, there is a need for alternative methods to prepare amides from various amines and acids. This need prompted us to explore coupling reactions activated by the Mukaiyama's reagent[9] (2-chloro-1-methylpyridinium iodide, CMPI). Its application to the preparation of a small library of 16 amides resulting from four acids and four secondary amines, including aromatic ones is reported.

CMPI is known to facilitate coupling reactions in the solution phase.[9] So, it is logical to explore its use for solid phase synthesis. For the preparation of polymer-supported amines, we adopted a modified procedure[10] starting from 2-(4-formyl-3-methoxyphenoxy)ethyl polystyrene. Reductive amination of the formyl resin with amines using $NaBH(OAc)_3$ and trimethyl orthoformate (TMOF) in 1,2-dichloroethane provides the corresponding polymer-supported secondary amine linked to the resin in nearly quantitative yield in 20 h at room temperature (Scheme 1). The coupling reactions of these secondary amines with different acids were conducted using Mukaiyama's reagent and in the presence of *N*,*N*-diisopropylethylamine (DIEA) in dichloromathane (DCM) at room temperature to provide the resin-linked amides, which after cleavage with TFA/DCM gave the desired amides in good purity (determined by HPLC and ^{1}H NMR) without purification.



Scheme 1

Table 1 Coupling reactions of polymer-supported amines (R) with acids (R′) by CMPI

Entry	R	R′	Conditions[a]	Purity/%[b]	yield/%[c]
1	$PhCH_2CH_2$	$PhCH_2CH_2$	A	95	82
2		$PhCH_2CH_2$	B	95	86
3		$PhCH_2CH_2$	C	95	85
4		4-BrPh	A	96	89
5		4-BrPh	C	95	87
6		4-OHCPh	A	95	90
7		3-O_2NPh	A	94	85
8	$Me_2N(CH_2)_3$	$PhCH_2CH_2$	A	95	88
9		4-BrPh	A	91	81
10		4-OHCPh	B	97	77
11		3-O_2NPh	B	90	85
12	Ph	$PhCH_2CH_2$	B	96	77
13		4-BrPh	B	88	58
14		4-OHCPh	A	92	57
15		3-O_2NPh	A	97	59
16	4-BrPh	$PhCH_2CH_2$	A	92	66
17		4-BrPh	A	86	42
18		4-OHCPh	A	91	53
19		3-O_2NPh	A	95	58

[a]Conditions: amine/acid/CMPI/DIEA = Method A 1:1.4:1.4:2.5, 24h, r.t. Method B 1:1.4:1.4:2.5, 48h, r.t.; Method C 1:2:2:3, 24h, r.t. [b]Purity was determined by HPLC using UV detection at 254 nm. [c]Yield was based on the original loading of the starting formyl resin.

The coupling reactions were typically completed in 24 h at room temperature. Longer reaction time (entries 1 and 2) and higher ratios of acids to amines (entries 1 and 3, 4 and 5) had no significant effect on yield or purity. The reactions gave good to high yields (77–90%) of the products from aliphatic amines and moderate to good yields (42–77%) from aromatic amines. The reaction was also tolerant to sensitive functional groups. For instance, the aldehyde group (entries 6, 10, 14 and 18) was not affected under these coupling conditions. It is noted that this method is good for both aliphatic and aromatic amines and acids, and it also has some advantages over existing methods in cost effectiveness as well as environmental friendliness by avoiding the use of phosphorus-containing reagents. The result we describe here for amide preparation is consistent with a recent report of use of the modified Mukaiyama's reagents for synthesis of hindered peptides.[11]

In conclusion, we have reported a new method to prepare amides on solid phase by coupling amines with various acids using the Mukaiyama's reagent under mild conditions. The amides are obtained after cleavage from the resin in high

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purity without purification. The process is illustrated by parallel synthesis of 16 amides from four amines and four acids. It is expected that the reaction will be used in the future to prepare amides in small molecule libraries.

Experimental

General procedure: 0.1 g of the amino resin was allowed to swell in DCM (10 ml) for 1 h. DIEA (2.8 equiv.), acid (1.4 equiv.) and CMPI (1.4 equiv.) were consecutively added to the resin. The reaction mixture was agitated on a mechanical shaker for 24 h. The solvent was removed by suction, the resin was washed with DCM (3 × 10 ml), MeOH (3 × 10 ml), and DCM (3 × 10 ml) and dried under vacuum. Cleavage of the amide from the resin was achieved by the action of TFA/DCM (10 ml, 1:1) for 20 h. Resin was removed by filtration and the solvent removed under reduced pressure to yield the amides. HPLC was performed on a reverse phase column using a gradient of 20/80 to 80/20 or 40/60 to 90/10 water: methanol (each containing 0.1% TFA).

The identity of all the amides was confirmed by ^{1}H NMR (300 MHz, CD_3OD) and LC-MS (ES mode) analysis.

N-(2-Phenylethyl)-3-phenylpropanamide[12] (entry 1). δ 7.25–7.11 (m, 10H), 3.34 (t, 2H, *J* = 7.8 Hz), 2.86 (t, 2H, *J* = 7.8 Hz), 2.69 (t, 2H, *J* = 7.5 Hz), 2.42 (t, 2H, *J* = 7.5 Hz); *m/z* 254.15 ($M+H^+$).

4-Bromo-N-(2-phenylethyl)benzamide (entry 5). δ 7.68–7.59 (m, 4H), 7.28–7.22 (m, 5H), 3.57 (t, 2H, *J* = 7.5 Hz), 2.90 (dd, 2H, *J* = 7.5 Hz); *m/z* 303.95, 305.95 ($M+H^+$); Found : [M^+] 303.0244. $C_{15}H_{14}NO^{79}Br$ requires 303.0259.

4-Formyl-N-(2-phenylethyl)benzamide[13] (entry 6). δ 10.04 (s, 1H), 7.99–7.90 (m, 2H), 7.75 (d, 1H, *J* = 8.4 Hz), 7.54 (d, 1H, *J* = 8.4 Hz), 7.28–7.19 (m, 5H), 3.63–3.56 (m, 2H), 2.95–2.88 (m, 2H); *m/z* 254.15 ($M+H^+$).

3-Nitro-N-(2-phenylethyl)benzamide[14] (entry 7). δ 8.62 (s, 1H), 8.36 (d, 1H, *J* = 8.1 Hz), 8.14 (d, 1H, *J* = 8.1 Hz), 7.70 (dd, 1H, *J* = 8.1, 8.1 Hz), 8.28–8.18 (m, 5H), 3.62 (t, 2H, *J* = 7.5 Hz), 2.93 (t, 2H, *J* = 7.5 Hz); *m/z* 271.15 ($M+H^+$).

N-(3,3-Dimethylaminopropyl)-3-phenylpropanamide (entry 8). δ 7.33–7.21 (m, 5H), 3.22 (t, 2H, *J* = 6.6 Hz), 2.95 (t, 2H, *J* = 7.5 Hz), 2.64–2.55 (m, 10H), 1.79–1.70 (m, 2H); *m/z* 235.15 ($M+H^+$); Found [M^+] 234.1742. $C_{14}H_{22}N_2O$ requires 234.1732.

4-Bromo-N-(3,3-dimethylaminopropyl)benzamide[15] (entry 9). δ 7.79 (dd, 2H, *J* = 6.6, 1.8 Hz), 7.67 (dd, 2H, *J* = 6.6, 1.8 Hz), 3.47 (t, 2H, *J* = 6.9 Hz), 2.80 (t, 2H, *J* = 7.8 Hz), 2.59 (s, 6H), 1.97–1.93 (m, 2H); *m/z* 285.15 and 287.15 ($M+H^+$).

4-Formyl-N-(3,3-dimethylaminopropyl)benzamide (entry 10). δ 10.16 (s, 1H), 8.10–8.02 (m, 4H), 3.55–3.48 (m, 2H), 2.45 (t, 2H, *J* = 6.6 Hz), 2.13 (s, 6H), 1.85–1.77 (m, 2H); *m/z* 235.15 ($M+H^+$); Found [M^+] 234.1374. $C_{13}H_{18}N_2O_2$ requires 234.1368.

3-Nitro-N-(3,3-dimethylaminopropyl)benzamide (entry 11). δ 8.68 (s, 1H), 8.39 (d, 1H, *J* = 8.4 Hz), 8.21 (d, 1H, *J* = 7.8 Hz), 7.74 (dd, 1H, *J* = 8.4, 7.8 Hz), 3.44 (t, 2H, *J* = 6.9 Hz), 2.42 (t, 2H, *J* = 7.5 Hz), 2.26 (s, 6H), 1.89–1.80 (m, 2H); *m/z* 252.15 ($M+H^+$); Found [M^+] 251.1306. $C_{12}H_{17}N_3O_3$ requires 251.1270.

N-Phenyl-3-phenylpropanamide[16] (entry 12). δ 7.48 (d, 2H, *J* = 8.7 Hz), 7.30–7.16 (m, 7H), 7.06 (dd, 1H, *J* = 8.7, 7.5 Hz), 2.99 (t, 2H, *J* = 7.5 Hz), 2.64 (t, 2H, *J* = 7.5 Hz); *m/z* 226.15 ($M+H^+$).

4-Bromo-N-phenylbenzamide[17] (entry 13). δ 7.84 (d, 2H, *J* = 7.2 Hz), 7.69–7.66 (m, 4H), 7.35 (dd, 2H, *J* = 7.5, 8.4 Hz), 7.14 (dd, 1H, *J* = 7.5, 7.5 Hz); *m/z* 275.95, 277.95 ($M+H^+$).

4-Formyl-N-phenylbenzamide[18] (entry 14). δ 10.19 (s, 1H), 8.22 (d, 2H, *J* = 8.4 Hz), 8.10 (d, 2H, *J* = 6.9 Hz), 7.91 (d, 2H, 7.2 Hz), 7.41 (dd, 2H, *J* = 7.5, 8.4 Hz), 7.18 (dd, 1H, *J* = 7.5, 7.2 Hz); *m/z* 226.15 ($M+H^+$).

3-Nitro-N-phenylbenzamide[17] (entry 15). δ 8.80 (s, 1H), 8.44 (d, 1H, *J* = 7.2 Hz), 8.33 (d, 1H, *J* = 7.5 Hz), 7.80–7.70 (m, 3H), 7.39 (dd, 2H, *J* = 7.8, 8.1 Hz), 7.17 (dd, 1H, *J* = 7.2, 7.5 Hz); *m/z* 243.05 ($M+H^+$).

N-(4-Bromophenyl)-3-phenylpropanamide (entry 16). δ 7.47–7.36 (m, 4H), 7.26–7.16 (m, 5H), 2.98 (t, 2H, *J* = 7.5 Hz), 2.64 (t, 2H, *J* = 7.5 Hz); *m/z* 303.95, 305.95 ($M+H^+$); Found [M^+] 303.0266. $C_{15}H_{14}NO^{79}Br$ requires 303.0259.

4-Bromo-N-(4-bromophenyl)benzamide[19] (entry 17). δ 7.82 (d, 1H, *J* = 8.4 Hz), 7.69–7.50 (m, 5H), 7.12 (d, 2H, *J* = 8.7 Hz); *m/z* 353.95, 355.95, 357.95 ($M+H^+$).

4-Formyl-N-(4-bromophenyl)benzamide (entry 18). δ 10.08 (s, 1H), 8.10–8.02 (m, 2H), 7.91 (d, 1H, *J* = 7.5 Hz), 7.69–7.60 (m, 3H), 7.52–7.47 (m, 2H); *m/z* 303.95, 305.95 ($M+H^+$); Found [M^+] 302.9868 $C_{14}H_{10}NO_2{}^{79}$ Br requires 302.9895.

3-Nitro-N-(4-bromophenyl)benzamide[20] (entry 19). δ 8.79 (s, 1H), 8.43 (d, 1H, *J* = 8.1 Hz), 8.31 (d, 1H, *J* = 7.8 Hz), 7.72 (dd, 1H, *J* = 7.8, 8.1 Hz), 7.68 (d, 2H, *J* = 8.7 Hz), 7.50 (d, 2H, *J* = 8.7 Hz); *m/z* 320.95, 322.95 ($M+H^+$).

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