Articles

Synthesis and Applications of a Novel Polymer-Supported EEDQ Reagent

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A simple synthetic protocol for a novel polymer-supported EEDQ reagent is reported. This reagent promotes solution-phase amide bond formation without any additives or base, as well as the selective coupling of aliphatic amines with acids in the presence of aromatic amines.

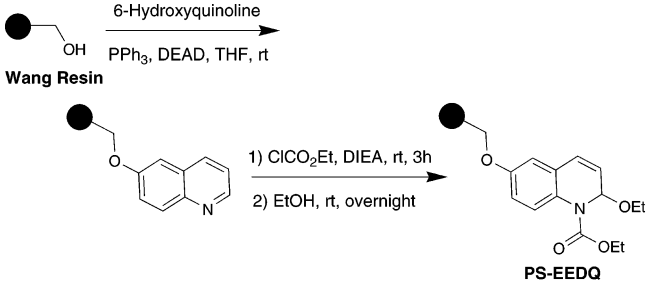
Introduction

In recent years, solution-phase parallel synthesis[1] using polymer-supported reagents has become an integral tool in medicinal chemistry. For a recent library synthesis, we required a polymer-supported amide bond-forming reagent that could be accessed in multigram quantities and did not require an additive or a base to activate the acid. Polymer-supported carbodimide[2] reagents generally require the addition of auxiliary nucleophiles (such as HOBt)[3] or a base (such as DMAP) to accelerate the amide bond formation. EEDQ[4] is a well-known coupling reagent that does not require any additive or base to form the amide bond. We envisioned that polymer-supported EEDQ would be as efficient as EEDQ in amide bond formation and would facilitate the efficient synthesis of library compounds. Two solid-supported reagents related to EEDQ have been reported: Poly-Q[5] and PS-IIDQ.[6] The synthesis of Poly-Q is labor intensive (it is made via a copolymerization process), and the reported loading[5] is low (0.3 mmol/g). Commercially available PS-IIDQ[6] is expensive, and its synthesis requires harsh reaction conditions. This article describes the straightforward synthesis and characterization of a high-loading polymer-supported EEDQ (PS-EEDQ) reagent.

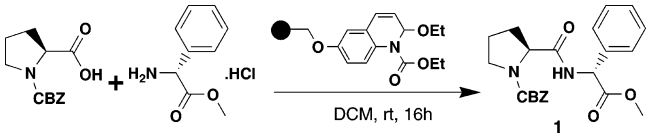
Results and Discussion

The synthesis of PS-EEDQ is outlined in Scheme 1. Commercially available Wang hydroxyl resin[7] was coupled to 6-hydroxyquinoline by a Mitsunobu[8] reaction using PPh_3 and DEAD in THF to afford the Wang resin-supported isoquinoline with 85% loading.[9] The Wang resin-supported isoquinoline was treated with ethyl chloroformate and diisopropylethylamine in dichloromethane (DCM) at 0 °C, followed by addition of ethanol and shaking at room temperature overnight to afford the PS-EEDQ reagent with 80% loading.[10]

Scheme 1. Synthesis of Polymer-Supported EEDQ (PS-EEDQ)



Scheme 2. PS-EEDQ Promoted Amide Bond Formation



Amide bond formation between CBZ-L-proline and 2-phenylglycine methyl ester (HCl salt) was used for optimization studies as shown in Scheme 2. Various amounts of PS-EEDQ (0.5−4 equiv) and solvents (DCM and CH_3CN) were studied, and the optimal yield was achieved by using 3 equiv of PS-EEDQ in DCM overnight to give product **1** in 80% yield. In the case of free amine substrates, the optimal amount of PS-EEDQ is 2 equiv. The chiral purity of product **1** was determined[11] and compared with the three other possible stereoisomers to establish that no racemization occurred during coupling. To explore the generality of PS-EEDQ, a small amide library was prepared as shown in Table 1. Coupling of CBZ-proline to tetrahydroisoquinoline (Table 1, entry 4), *o*-anisidine (Table 1, entry 7), *p*-anisidine (Table 1, entry 10), and methyl 4-aminobenzoate (Table 1, entry 13) resulted in good yields of products **4**, **7**,[12] **10**,[13] and **13**, respectively. Coupling of phenylacetic acid to 2-phenylgly-

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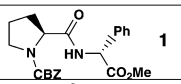
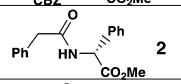
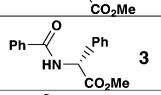
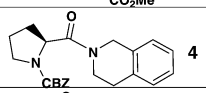
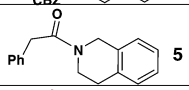
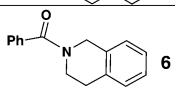
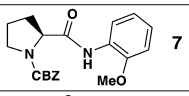
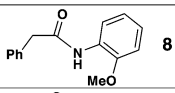
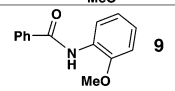
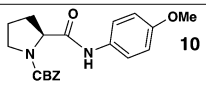
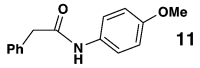
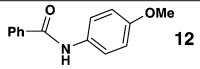
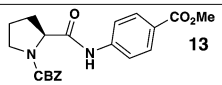
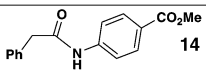
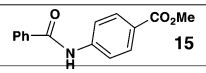
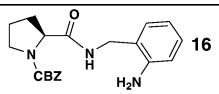
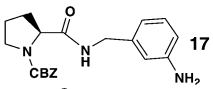
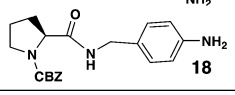
Table 1. Coupling of Acids with Amines and Anilines Using PS-EEDQ

Entry	Amine	Acid	Product[a]	Purity (HPLC)	Yield (Isolated)
1	(R)-2-Phenylglycine methyl ester HCl	Carbobenzyloxy-L-proline	 **1**	100%	80%
2	(R)-2-Phenylglycine methyl ester HCl	Phenylacetic acid	 **2**	100%	80%
3	(R)-2-Phenylglycine methyl ester HCl	Benzoic acid	 **3**	100%	32%
4	1,2,3,4-Tetrahydroisoquinoline	Carbobenzyloxy-L-proline	 **4**	100%	73%
5	1,2,3,4-Tetrahydroisoquinoline	Phenylacetic acid	 **5**	96%	80%
6	1,2,3,4-Tetrahydroisoquinoline	Benzoic acid	 **6**	91%	52%
7	*o*-Anisidine	Carbobenzyloxy-L-proline	 **7**	100%	81%
8	*o*-Anisidine	Phenylacetic acid	 **8**	100%	77%
9	*o*-Anisidine	Benzoic acid	 **9**	100%	78%
10	*p*-Anisidine	Carbobenzyloxy-L-proline	 **10**	100%	85%
11	*p*-Anisidine	Phenylacetic acid	 **11**	100%	87%
12	*p*-Anisidine	Benzoic acid	 **12**	100%	82%
13	Methyl 4-aminobenzoate	Carbobenzyloxy-L-proline	 **13**	100%	73%
14	Methyl 4-aminobenzoate	Phenylacetic acid	 **14**	100%	65%
15	Methyl 4-aminobenzoate	Benzoic acid	 **15**	No product	0%

[a] All reactions were performed on a 0.1 mmol scale in 5 mL of DCM for 16 h.

Table 2. Coupling of Acids with Diamines Using PS-EEDQ

Entry	Amine	Acid	Product[a]	Purity (HPLC)	Yield (isolated)
1	2-Aminobenzylamine	Carbobenzyloxy-L-proline	 **16**	100%	75%
2	3-Aminobenzylamine	Carbobenzyloxy-L-proline	 **17**	100%	76%
3	4-Aminobenzylamine	Carbobenzyloxy-L-proline	 **18**	100%	71%

[a] All reactions were performed on a 0.1 mmol scale in 10 mL of DCM for 16 h.

cine methyl ester (Table 1, entry 2), tetrahydroisoquinoline (Table 1, entry 5), *o*-anisidine (Table 1, entry 8), *p*-anisidine (Table 1, entry 11), and methyl 4-aminobenzoate (Table 1, entry 14) also gave acceptable yields of products **2**,[14] **5**,[15]

Table 3. CBZ-L-Proline Coupling to 3-Amino-benzylamine Using PS Reagents

entry	coupling reagent	base	solvent	product ratio (bis/mono)[a,b]
1	PS-EEDQ	no base	DCM	0/100
2	PS-Carbodimide	DIEA	DCM	13/87
3	IIDQ-Polystyrene	no base	DCM	10/90

[a] All reactions were performed on a 0.1 mmol scale in 10 mL of DCM for 16 h. [b] The ratio of bis/mono was determined by HPLC.

8,[16] **11**,[17] and **14**,[17] respectively. PS-EEDQ-mediated coupling reactions of anilines with benzoic acid (Table 1, entries 9 and 12) resulted in good yields of products **9**[18] and **12**.[19] However, PS-EEDQ coupling of benzoic acid with 2-phenylglycine methyl ester (Table 1, entry 3) and tetrahydroisoquinoline (Table 1, entry 6) gave poor yields of **3**[20] and **6**.[21] No product (**15**) was obtained during the PS-EEDQ coupling of methyl 4-aminobenzoate with benzoic acid (Table 1, entry 15). It is not clear why benzoic acid performs poorly under these conditions.

After successfully demonstrating the coupling of amines and anilines with various acid substrates using PS-EEDQ (Table 1), we turned our attention to the selective coupling of diamines to acids. We chose aminobenzylamine regioisomers which contain one aromatic and one aliphatic amine group, and the results of these substrates coupling to CBZ-L-proline using PS-EEDQ are shown in Table 2. In all the cases, PS-EEDQ gave pure products (**16**, **17**, and **18**) in greater than 70% yield, and no bis-coupled product was observed. In contrast, coupling of 3-aminobenzylamine with CBZ-L-proline using PS-carbodimide with DIEA (Table 3, entry 2) produced the mono- and bis-coupled products in a 7:1 ratio in 60% yield. In the case of PS-IIDQ-mediated (Table 3, entry 3) coupling of 3-aminobenzylamine with CBZ-L-proline, the mono- and biscoupled products were formed in 8:1 ratio in 80% isolated yield.

In conclusion, we have developed a scalable, inexpensive, and simple synthetic method for a novel polymer-supported EEDQ reagent and have shown that this reagent is a very efficient and versatile amide bond-forming reagent. PS-EEDQ is also capable of forming amide bonds between acids and aliphatic amines in the presence of aromatic amines. PS-EEDQ resin retains its reactivity for several months if it is stored in the refrigerator. We have found that the PS-isoquinoline recovered from PS-EEDQ after completion of the reaction can be recycled to provide PS-EEDQ without any loss of its reactivity to form amide bonds.

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Supporting Information Available. Experimental procedures and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans.* **2000**, *1*, 3815−4195.
(2) Keck, G. E.; Sanchez, R.; Wager, C. A. *Tetrahedron Lett.* **2000**, *41*, 8673−8676.
(3) Carpino, L. A. *J. Am. Chem. Soc*. **1993**, *115*, 4397−4398.
(4) Belleau, B.; Malek, G. *J. Am. Chem. Soc.* **1968**, *90*, 1651−1652.
(5) Brown, J.; Williams, R. E. *Can. J. Chem.* **1971**, *49*, 3765−3766.
(6) Valuer, E.; Bradley, M. *Chem. Commun.* **2005**, 1164−1166.
(7) (a) Wang, S. S. *J. Am. Chem. Soc.* **1973**, *95*, 1328−1333. (b) Purchased from Novabiochem.
(8) (a) Richter, L. S.; Gadek, T. R. *Tetrahedron Lett.* **1994**, *35*, 4705−4706. (b) Krchnak, V.; Flegelova, Z.; Weichsel, A. S.; Lebl, M. *Tetrahedron Lett.* **1995**, *36*, 6193−6196.
(9) Quinoline loading was determined by nitrogen elemental analysis (1.46 mmol/g). Loading was also calculated by cleavage of quinoline from the resin with 50% TFA in DCM for 2 h and then vacuum concentration to provide 85% recovery.
(10) Loading of EEDQ on resin was calculated by coupling of phenylpropionic acid (1 equiv) with cyclohexylamine (1 equiv) with PS-EEDQ (1.1 equiv) and calculation of the yield of the product (80%). Loading was also confirmed by nitrogen elemental analysis which showed the loading at 1.35 mmol/g. The formation of EEDQ on the resin was confirmed by the presence of a characteristic absorption band of the carbamate moiety at 1701 cm^{-1} in the IR (KBr) spectra.
(11) Chiral purity of *Z*-Pro-D-Phg-OMe (**1**, 99.9%) was determined by using Chiralpak AD-H column and it's RT (10.41 min) was compared with the three other possible isomers *Z*-Pro-Phg-OMe (15.16 min), *Z*-D-Pro-Phg-OMe (7.51 min), and *Z*-D-Pro-D-Phg-OMe (8.63 min).
(12) O'Brien, P.; Warren, S. *J. Chem. Soc.* **1996**, *17*, 2129−2138.
(13) Rhyoo, H. Y.; Yoon, Y. A.; Park, H. J.; Chung, Y. K. T. *Tetrahedron Lett.* **2001**, *42*, 5045−5048.
(14) Carboni, C.; Quaedflies, P. J. L. M.; Broxterman, Q. B.; Linda, P.; Gardossi, L. *Tetrahedron Lett*. **2004**, *45*, 9649−9652.
(15) Venkov, A. P.; Statkova-Abeghe, S. M. *Tetrahedron* **1996**, *52*, 1451−1460.
(16) Langlois, M.; Curtat, S. *Tetrahedron Lett.* **1999**, *40*, 8563−8566.
(17) Slobodan, D. P. J. *J. Serb. Chem. Soc.* **1986**, *51*, 395−403.
(18) Yudao, M. *Synthesis* **2003**, 2886−2889.
(19) Md-Wahab, K. *Tetrahedron* **2005**, *61*, 11204−11210.
(20) Yadav, J. S.; Reddy, B. V. S.; Reddy, K. S. *Synlett* **2002**, 468−470.
(21) Al-Hiari, Y. M. *J. Het. Chem*. **2005**, *42*, 647−659.

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