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Tetrahedron Letters 44 (2003) 9267–9269

TETRAHEDRON
LETTERS

Preparation and applications of a polymer-supported phosphoryl azide☆

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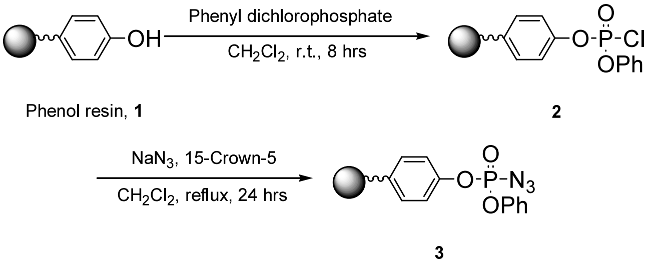
Received 22 September 2003; revised 10 October 2003; accepted 13 October 2003

Abstract—A polymer-supported diphenylphosphoryl azide was prepared. This polymer-supported version of DPPA is useful due to its lower toxicity, moisture tolerance and ease of workup after reaction. The synthetic application of this solid-phase reagent was explored by conversion of a variety of carboxylic acids to urethanes and ureas through Curtius rearrangement reactions. Carboxylic acids bearing different functional groups (aromatic, aliphatic and heterocyclic carboxylic acids) were subjected to the reaction. The corresponding products were isolated with satisfactory yields.

Carboxylic acids and their derivatives can be converted to amines through molecular rearrangement.[1,2] Diphenylphosphoryl azide (DPPA) has been widely used for organic synthesis since T. Shioiri and S. Yamada et al. used DPPA as a modified azide to conduct Curtius reactions in 1972.[3,4] However, toxicity considerations limit its usage and cause environmental problems. The high boiling point of DPPA creates additional difficulties in workup and purification after reaction.[5] The relative sensitivity of commercial DPPA to moisture and oxidizing agents necessitates careful storage. Recent technological advancements in polymer-supported reagents provide solutions to these drawbacks. Using polymers with the Curtius reaction has precedence in drug delivery and combinatorial chemistry. Several reports of polymer-bound carboxylic acids undergoing rearrangement to polymer-bound isocyanates have appeared,[6,7] as well as papers describing polymer-bound nucleophiles capturing isocyanate intermediates generated by the Curtius reaction.[8,9] Herein we report the synthesis of a polymer-supported DPPA (Scheme 1).[10]

Phenol resin **1** (1.5 mmol/g, Advanced ChemTech) was first swelled in dichloromethane under a nitrogen atmosphere for 5 min, then 5.0 equiv. phenyl dichlorophosphate was added at room temperature and stirred for 8 h.[11] After removal of excess phenyl dichlorophosphate by a simple wash with dichloromethane under nitrogen atmosphere, the phenyl chlorophosphate loaded resin **2** was converted to solid-phase supported DPPA **3** by treatment with 3.0 equiv. sodium azide and 3.0 equiv. crown ether (15-crown-5) in dichloromethane under reflux for 24 h.[12] The crown ether was a necessary phase-transfer reagent to provide maximum reaction efficiency. The excess sodium azide and crown ether were removed by filtration and washing with dichloromethane and a small amount of distilled water. After drying under vacuum overnight, the polymer-supported azide **3** was ready to use. The IR spectrum of polymer-supported DPPA shows a strong azide absorption peak at 2168 cm^{-1}, which is identical to that of DPPA. This solid-phase supported DPPA is quite stable at room temperature. There is no obvious change observed in the IR spectrum after one month of storage in air.



Scheme 1. Synthesis of polymer-supported DPPA.

☆ Supplementary data associated with this article can be found at doi:10.1016/j.tetlet.2003.10.066

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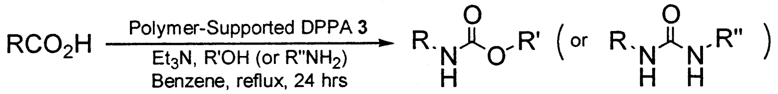
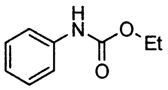
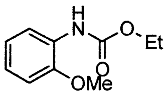
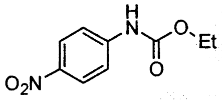
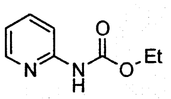
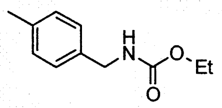
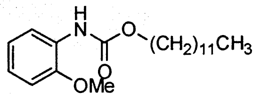
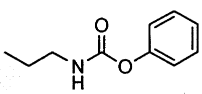
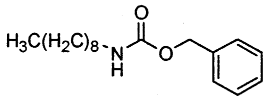
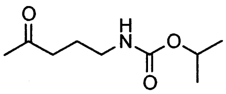
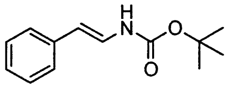
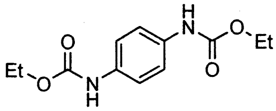
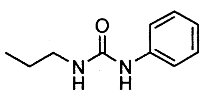
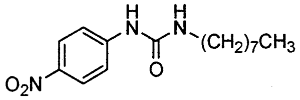
doi:10.1016/j.tetlet.2003.10.066

Table 1. Urethane or urea synthesized by polymer-supported DPPA



Entry	RCO_2H	R'OH (or R"NH_2)	Product	Yield[a,b] (%)
1	Benzoic acid	Ethanol		53[13]
2	*o*-Anisic acid	Ethanol		72[13]
3[b]	4-Nitrobenzoic acid	Ethanol		80[13]
4	Picolinic acid	Ethanol		48[14]
5	*p*-Tolylacetic acid	Ethanol		46[15]
6	*o*-Anisic acid	Dodecanol		52[16]
7	Butyric acid	Phenol		52[17]
8	Decanoic acid	Benzyl alcohol		34[18]
9	4-Acetylbutyric acid	2-Propanol		47[19]
10	*trans*-Cinnamic acid	*t*-Butanol		54[4]
11	Terephthalic acid [c]	Ethanol		36[20]
12	Butyric acid	Aniline		45[21]
13	4-Nitrobenzoic acid	Octylamine		41[22]

[a] Isolated yields after column chromatography. (Since it is hard to estimate the azide loading on polymer-supported DPPA, a little excess carboxylic acid was used in the reactions to calculate the yields after two steps.)

[b] All the product exhibited physical and spectral (NMR, IR and MS) properties in accord with the assigned structures.

[c] The ratio between polymer-supported DPPA and terephthalic acid is 2.2 : 1.

The synthetic use of the polymer-supported phosphoryl azide was explored by converting a variety of carboxylic acids to urethanes or ureas through Curtius rearrangement.[4] A typical experimental procedure for the synthesis of ethyl *p*-nitrocarbanilate (entry 3 in Table 1) follows: Polymer-supported DPPA (1.0 g, ~1.5 mmol, 1.0 equiv., based on fully azide-loaded resin) was swelled in benzene (10 mL) under a nitrogen atmosphere for 5 min. To this suspension were added 4-nitrobenzoic acid (0.30 g, 1.8 mmol, 1.2 equiv.) and triethylamine (0.21 g, 2.0 mmol, 1.4 equiv.) at room temperature. The mixture was heated to reflux for 30 min. Ethanol (0.15 mL, 2.5 mmol, 1.7 equiv.) was added and the reaction was heated at reflux for 24 h. After cooling to room temperature, the resin, including unreacted DPPA and phosphorous derivatives still linked on the resin, was removed by filtration and washed with ethyl acetate (100 mL). The combined filtrates containing the desired ethyl *p*-nitrocarbanilate were washed with aqueous sodium hydroxide (1 M, 3×30 mL), distilled water (3×30 mL) and brine (30 mL). After drying ($MgSO_4$), solvent was removed under vacuum to afford the crude product. Purification was performed on silica-gel column chromatography (1:1 petroleum/diethyl ether) to give pure ethyl *p*-nitrocarbanilate (0.25 g, 80% yield). Following similar procedures, carboxylic acids bearing different functional groups (aromatic, aliphatic and heterocyclic carboxylic acids) were subjected to the reaction, and corresponding urethanes and ureas were obtained. The results are listed in Table 1. The overall yields after two steps (polymer-supported DPPA and urethane or urea syntheses) are serviceable (yield: 34–80%) and the crude products, even before final purification are uncontaminated by phosphoryl ester byproducts.

In conclusion, the first synthesis of solid-phase supported DPPA had been achieved. This new reagent may have considerable use in synthetic chemistry seems based on its moisture tolerance, lower toxicity and easy removal after the reactions.

Supplementary Data

Experimental procedures and spectroscopic data are available for the polymeric azide **3** and for all products reported in Table 1. The supplementary material is available online with the paper in ScienceDirect.

Acknowledgements

The support of Miami University through its Committee on Faculty Research is gratefully acknowledged.

References

1. Buehler, C. A.; Pearson, D. E. *Survey of Organic Syntheses*; Wiley-Interscience: New York, 1970; pp. 494–503.
2. Shioiri, T. In *Comprehensive Organic Synthesis*, Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 6, pp. 795–828.
3. Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203–6205.
4. Ninomiya, K.; Shioiri, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151–2157.
5. Taylor, R. T.; Paupaiboon, U. *Tetrahedron Lett.* **1998**, *39*, 8005–8008.
6. Richter, L. S.; Andersen, S. *Tetrahedron Lett.* **1998**, *39*, 8747–8750.
7. Shao, H.; Colucci, M.; Tong, S.; Zhang, H.; Castelhano, A. L. *Tetrahedron Lett.* **1998**, *39*, 7235–7238.
8. Sunami, S.; Sagara, T.; Ohkubo, M.; Morishima, H. *Tetrahedron Lett.* **1999**, *40*, 1721–1724.
9. Migawa, M. T.; Swayze, E. E. *Org. Lett.* **2000**, *2*, 3309–3311.
10. For syntheses of both polymer-supported DPPA and urethanes (or ureas), all manipulations were performed in oven-dried glassware under a nitrogen atmosphere unless otherwise mentioned. All solvents and reagents were dried or purified using standard procedures and distillated freshly before use. Standard workup included washing with water followed by brine. The organic phase was dried over magnesium sulfate, and concentrated in vacuo. Column chromatography was performed on silica gel (Natland International Corp. 200–400 mesh) using the indicated solvents. TLC analyses were carried out using C4 silica gel plates (Silicycle Inc.). Uncorrected melting points were determined with a Gallenkamp melting point apparatus. ^{1}H and ^{13}C NMR spectra were recorded at 200 MHz (Bruker Avance 200) in $CDCl_3$ or acetone-d_6 (Aldrich). IR spectra were determined as neat film (using NaCl plate) or KBr pellet on a Perkin–Elmer 1600 FT-IR spectrophotometer. MS spectra were performed by HP 5890 series II Gas chromatograph and 5971 series mass selective detector.
11. Thomas, A. V. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed. Diphenyl Phosphorochloridate; Wiley: New York, 1995; pp. 2245–2247.
12. Thomas, A. V. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A.. Ed. Diphenyl Phosphorazidate; Wiley: New York, 1995; pp. 2242–2245.
13. NMR spectral properties are the same as those exhibit in Sadtler® standard NMR spectrum.
14. Shriner, R. L.; Child, R. G. J. *J. Am. Chem. Soc.* **1952**, *74*, 549–550.
15. Waller, F. J. EP0195515, *Eur. Pat. Appl.* 1986, 31.
16. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.86 (t, $J=6.9$ Hz, 3H), 1.24 (b, 18H), 1.66 (m, 2H), 3.85 (s, 3H), 4.14 (t, $J=6.7$ Hz, 2H), 6.82 (m, 1H), 6.96 (m, 2H), 7.2 (m, 1H), 8.1 (b, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.08, 22.66, 25.86, 28.96, 29.28, 29.32, 29.52, 29.56, 29.60, 29.62, 31.89, 55.61, 65.30, 109.93, 118.13, 121.11, 122.56, 127.77, 147.52, 153.63. FT-IR (cm^{-1}): 3436, 2924, 2853, 1736, 1604, 1531, 1461, 1207, 1130.
17. Yamamoto, I.; Takahashi, Y. and Kyomura, N. DE2545389, *Ger. Offen.* 1976, 86.
18. Yadav, J. S.; Reddy, B. V. S.; Reddy, G. S. K. K. *New J. Chem.* **2000**, *24*, 571–573.
19. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.19 (d, $J=6.2$ Hz, 6H), 1.72 (m, 2H), 2.13 (s, 3H), 2.47 (t, $J=7.1$ Hz, 2H), 3.14 (q, $J=6.5$ Hz, 2H), 4.65 (b, 1H), 4.86 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.13, 23.96, 29.98, 40.23, 40.69, 67.96, 156.40, 208.42. FT-IR (cm^{-1}): 2923, 1710, 1528, 1252, 1112.
20. Miyagi, Y.; Banjyo, N.; Yamamura, E. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 857–858.
21. Izdebski, J.; Pawlak, D. *Synthesis* **1989**, *6*, 423–425.
22. Wilcox, C. S.; Kim, E.; Romano, D.; Kuo, L. H.; Burt, A. L.; Curran, D. P. *Tetrahedron* **1995**, *51*, 621–634.