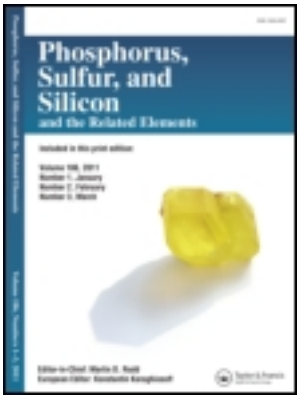

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Synthesis of Phosphinic Acid Pseudodipeptides of C_2 -Symmetry

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SYNTHESIS OF PHOSPHINIC ACID PSEUDODIPEPTIDES OF C_2-SYMMETRY

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Abstract *Treatment of aromatic aldehydes with ammonia and hypophosphorus acid gave C_2-symmetric 1-aminoarylmethylphosphinic acids. The latter compounds, activated in the presence of hexamethyldisilazane (HMDS) or trimethylsilyl chloride (TMSCl), successfully reacted with methyl acrylate to afford symmetric pseudodipeptides. The applied synthetic approach is briefly outlined here.*

Keywords 1-Aminoalkylphosphinic acids; C_2-symmetry; diastereoisomers; hypophosphorus acid; pseudodipeptides

INTRODUCTION

Aminoalkylphosphinic acids are the phosphorus analogues of natural amino acids that have potential biological activity and strong coordination ability. Because of the tetrahedral structure of the phosphinic acids R_2PO_2H (R = alkyl, aryl), they are considered to mimic the transition states in hydrolysis of carboxylic esters, amides, and peptides.[1] The incorporation of the phosphinic moiety into the peptide structure has been studied as efficient approach for developing highly potent and selective inhibitors of various proteolytic enzymes, particularly metalloproteases. Aminophosphinic acid derivatives, built on a C_2-symmetry axis homodimer structural motif, are also attractive drugs that target the protease of the human immunodeficiency virus, HIV-1 aspartic protease.[2]

RESULTS AND DISCUSSION

As a part of our effort to introduce novel methods for the synthesis of organophosphorus compounds, we have reported a convenient and simple method for the synthesis of novel 1-aminophosphinic acids containing two phosphinic moieties with a C_2-symmetry axis (Scheme 1). The aminobisphosphinic acids **2** were synthesized in the reaction of

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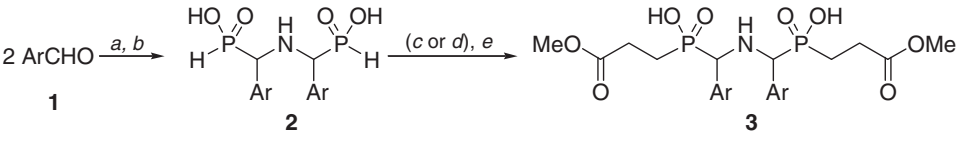

Entry	Ar	Yield (%)	
		HMDS (conditions *c*)	TMSCl (conditions *d*)
3a	Ph	50	40
3b	*p*-ClC_6H_4	60	52
3c	*p*-FC_6H_4	40	35
3d	*p*-$MeOC_6H_4$	58	50
3e	*p*-MeC_6H_4	54	45
3f	β-Naphthyl	57	48

Scheme 1 Reagents and conditions: (a) NH_4OH_{aq}, reflux, 5h; (b) H_3PO_2 (5 equiv.), reflux (ethanol), 10 h, then washing with ethanol/water (9:1); (c) HMDS, 110°C; (d) TMSCl, NEt_3, CH_2Cl_2, 0°C, stirred under Ar, 3h; (e) methyl acrylate, 50°C, stirred 12 h, then MeOH. The yield of isolated products **3**, obtained by two activation methods from **2**, are compared.

aromatic adehydes **1** with ammonia, followed by treatment with anhydrous hypophosphorus acid.[3] The difference in solubility allowed us to readily separate the obtained mixture of diastereoisomers by simple washing.

C_2-Symmetric phosphinic acid dipeptides **3** were obtained by the Michael addition of **2** to methyl acrylate. Both applied activation/silylation agents: hexamethyldisilazane (procedure *c*, Scheme 1) and trimethylsilyl choride (procedure *d*) gave target compounds in moderate yields.

REFERENCES

1. Kukhar, V. P.; Hudson, H. R. In *Aminophosphonic and Aminophosphinic Acids*; John Wiley & Sons: Chichester, UK, 2000.
2. Collinsova, M.; Jiracek, J. *Curr. Med. Chem.* **2000,** *7*, 629–647.
3. Kaboudin, B.; Saadati, F. *Tetrahedron Lett*. **2009,** *50*, 1450–1452.