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Phosphine Mediated Synthesis of 2-Methylidene-3-Amino Esters and Ketones

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Abstract:

A facile procedure for the generation of the title compounds is described.

In connection with our research on the design and synthesis of peptide mimetics,[1] we required a facile versatile synthesis of 2-methylidene-3-aminopropanoates.[2,3,4] Based on the work of Morita,[5,6] we have investigated the phosphine mediated synthesis of the title compounds. The synthetic scheme employed is outlined below. Table 1 displays the scope and limitations of this reaction.

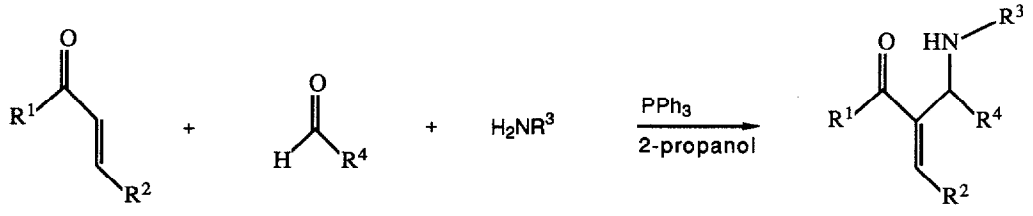

Table 1.

Entry	R^1	R^2	R^3	R^4	% Yield
1	MeO	H	Ts	Ph	98
2	Me	H	Boc	Ph	50
3	MeO	H	Ts	Ph	98[7]
4	MeO	H	Ts	nPr	80
5	MeO	H	CBZ	Ph	53
6	MeO	Me	Ts	Ph	0[8]

A typical procedure is described: 0.25mmol of p-toluenesulphonamide, 0.25mmol benzaldehyde, and 0.25mmol methylacrylate are dissolved in 250ul of 2-propanol. To this solution is added 0.8 mole % (0.002mmol) of PPh_3. This mixture was heated at 40° C for 40 hrs.. Removal of the solvent in vacuo, followed by flash 9 chromatography (solvent 30:1 CH_2Cl_2:MeOH), afforded the desired product in 98% yield. The products in entries 2, 4, and 5 were readily purified using flash chromatography (solvents systems varied between 50:1 and 10:1 CH_2Cl_2:MeOH).

In summary, an experimentally simple preparation for a variety of 2-methylidene-3-amino esters

and ketones is described. This procedure is compatible with both aromatic and aliphatic (entry 4) imines which bear an electron withdrawing group on nitrogen. Both methylacrylate and methylvinyl ketone (entry 2) can be utilized, however, β-substitution is not tolerated (entry 6). It should be noted that these α-aminoalkyl acrylates are precursors to optically active β-amino acids[3] and the corresponding azetidinones.

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7. This reaction was run using Chiraphos, no asymmetric induction was observed.
8. No product was observed after 7 days.

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