Simple Esterification of Protected Amino Acids using Polystyrene-Bound TBD and Microwave Heating

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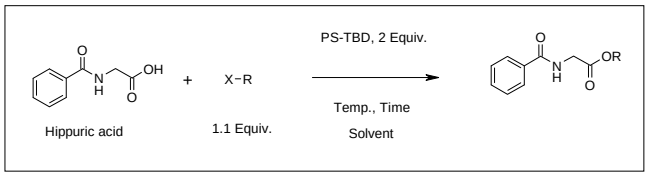
Summary

Microwave-assisted esterification of protected amino acid derivatives was performed using alkyl halides and polystyrene supported TBD[1,2] (*Fig. 1*) as base. The preferred solvents were THF or acetonitrile. The products were obtained in good yields and high purity. Short reaction time, 10 minutes, and easy work-up, filtration and evaporation, constituted a convenient procedure. Benzyl, allyl, phenacyl, and alkyl esters, all important and commonly used derivatives in peptide synthesis, were synthesised.

Results and discussion

Optimisation

Hippuric acid and two halides, benzyl bromide and propyl iodide, were chosen in order to optimise the reaction (*Scheme 1*). When the optimal temperatures, reaction times and equivalents were established, the choice between two solvents, THF and acetonitrile, remained: By using THF as solvent, the resulting yields were substantially higher than when acetonitrile was used as solvent, but the purities were somewhat lower (*Table 1*). Both the higher yields and the somewhat lower purities may reflect the fact that the swelling of the resin is larger in THF than in acetonitrile. THF was chosen as solvent in the subsequent reactions.



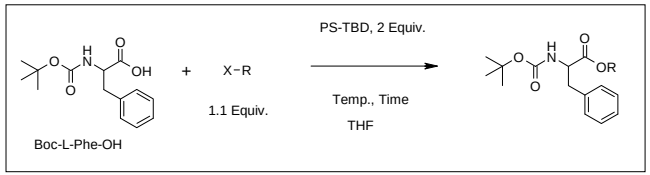
Scheme 1

Entry	Halide	Solvent	Temp. °C	Time min.	Conversion, % [3]	Isolated yield %	Purity Isolated product % [3]
1		MeCN	120	10	98	65	99
2		THF	120	10	98	80	96
3		MeCN	140	10	99	77	99
4		THF	140	10	99	90	97

Table 1

Two reaction sequences

The protected amino acid derivatives, Boc-L-Phe-OH (*Scheme 2*) and Z-D-Lys(Boc)-OH (*Scheme 3*), were esterified using PS-TBD as base. Five halides were used in the two reaction sequences, yielding the corresponding benzyl, allyl, phenacyl, propyl phthaloyl and propyl esters. The obtained conversions were determined by analysing the reaction mixtures by LC-MS. After the work-up, which consisted of a simple filtration, washing of the solids and solvent evaporation, the products were weighed and analysed again by LC-MS (*Tables 2 & 3*). The observed conversions were high through both reaction sequences, 89-99%, and the purities of the isolated materials were in the same range.



Scheme 2

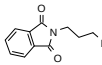
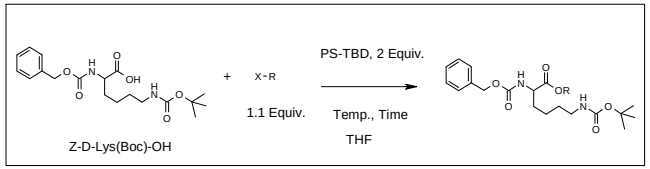
Entry	Halide	Temp. °C	Time min.	Conversion, % [4]	Isolated yield %	Purity Isolated product % [4]
5		120	10	99	84	94
6		120	10	97	88	96
7		120	10	97	82	98
8		150	10	92	99	90
9		140	10	99	82	99

Table 2



Scheme 3

Entry	Halide	Temp. °C	Time min.	Conversion, % [4]	Isolated yield %	Purity Isolated product % [4]
10		120	10	97	90	96
11		120	10	97	74	90
12		120	10	98	76	95
13		150	10	89	99	88
14		140	10	98	93	93

Table 3

General experimental procedure

To a 2-5 mL microwave reaction vial with 496 mg PS-TBD (1.21 mmol/g, 0.60 mmol) was added 3.6 mL solvent (THF or acetonitrile), 0.3 mmol N-protected amino acid and 0.33 mmol halide. The vial was capped and heated in Initiator™ Sixty for 10 minutes at the temperatures stated in *Tables 1-3*. After cooling, the vial was decapped and the mixture was filtered. The resin was washed with 5 x 3 mL solvent (THF or acetonitrile) and the combined filtrate and washings were concentrated and dried under vacuum. All products were analysed by LC-MS and, during the optimisation sequence, ^{1}H-NMR.

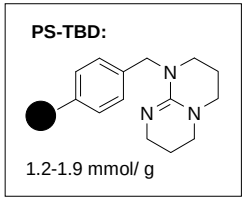


Fig. 1

RN

References & notes:

1. 1,5,7-triazabicyclo[4.4.0]dec-5-ene
2. PS-TBD, Biotage Technical Note
3. LC-MS, λ = 230 nm
4. LC-MS, λ = 210 nm

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