



## Technical Support Information Bulletin 1147

### Coupling Dialkylglycines

Due to their steric hindrance, dialkyl glycines often are difficult to couple. In general, coupling of common amino acids to the amine group of dialkyl amino acids can be achieved in satisfactory yields using standard coupling procedures,<sup>1</sup> although the reactions may be slower.<sup>2</sup> Coupling of the acid group of dialkylglycines is more difficult, however. Standard coupling methods often fail completely or produce very low yields. 2-Aminoisobutyric acid (Aib) and 1-aminocyclohexane carboxylic acid (Ac<sub>6</sub>c) can be coupled after conversion to the corresponding acid fluorides.<sup>3</sup> Even Aib-Aib couplings produce good yields under these conditions, although Ac<sub>6</sub>c-Ac<sub>6</sub>c couplings are low yielding. Coupling of dipropylglycine (Dpg) and dibutylglycine (Dbg) have been reported using dicyclohexylcarbodiimide-hydroxybenzotriazole (DCC-HOBt) activation,<sup>1,2</sup> but these reactions may require as long as 48 hours and produce by-products.

#### Coupling by Acid Fluorides<sup>4</sup>

1. Swell the resin in dimethylformamide (DMF), then filter the resin.
2. Add 3 equivalents of 0.3 M solution of the amino acid fluoride in DMF.
3. Add one equivalent of diisopropylethylamine (DIPEA).
4. Shake the mixture for 20 to 30 minutes.
5. Filter and wash the resin with DMF.
6. Repeat the coupling procedure if needed to achieve complete reaction.

#### Coupling by DCC-HOBt Activation<sup>2</sup>

1. Suspend the resin in DMF.
2. In a separate flask, add 1.5 equivalents of the N-protected amino acid dissolved in DMF.
3. Cool the solution in an ice bath.
4. Add 1.5 equivalents of HOBt and 1.5 equivalents of DCC.
5. Stir the mixture for 5 minutes, then filter the cold solution into the flask containing the resin.
6. Shake the mixture at room temperature for 48 hours.
7. Filter and wash the resin with DMF and DCM.

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<sup>1</sup> Hardy, P. M.; Lingham, I. N. *Int. J. Peptide Protein Res.* **1983**, *21*, 392.

<sup>2</sup> Prasad, S.; Rao, R. B.; Bergstrand, H.; Lundquist, B.; Becjker, E. L.; Balaram, P. *Int. J. Peptide Protein Res.* **1996**, *48*, 312.

<sup>3</sup> Yokum, T. S.; Elzer, P. H.; McLaughlin, M. L. *J. Med. Chem.* **1996**, *39*, 3603.

<sup>4</sup> Wenschuh, H.; Beyermann, M.; Krause, E.; Brudel, M.; Winter, R.; Schumann, M.; Carpino, L. A.; Bienert, M. *J. Org. Chem.* **1994**, *59*, 3275.