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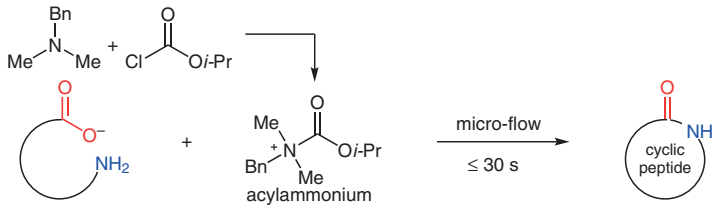
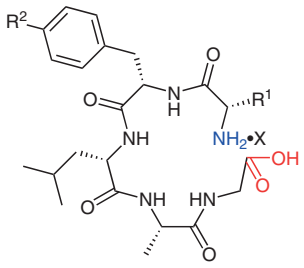
Peptide Cyclization by the Use of Acylammonium Species
*Angew. Chem. Int. Ed.* **2023**, *62*, e202300647 DOI: 10.1002/anie.202300647.

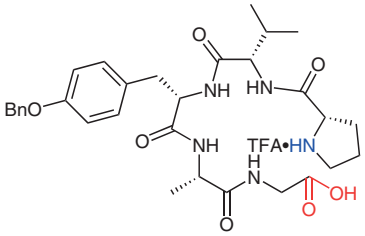
# Efficient Method for Cyclic Peptide Synthesis Mediated by Acylammonium Species

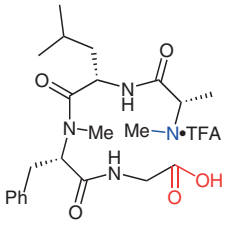



**Selected examples:**




- **1**: $R^1$ = Me, $R^2$ = OBn, X = TFA
- **2**: $R^1$ = 3-indolyl, $R^2$ = H, X = HCl

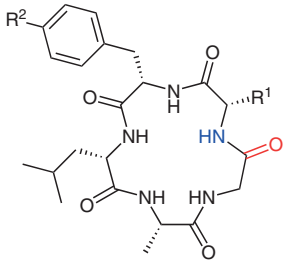


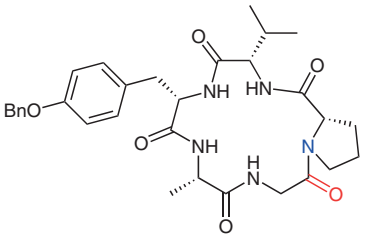

$ClCO_2i$-Pr (2 equiv)
$Me_2NBn$ (2 equiv)
KOH (2 equiv)
MeCN–$H_2O$ (3.3 mM)
60 °C, 30 s (**1**) or 10 s (**2**)

$ClCO_2i$-Pr (2 equiv)
$Me_2NBn$ (2 equiv)
KOH (2 equiv)
MeCN–$H_2O$ (3.3 mM)
60 °C, 10 s

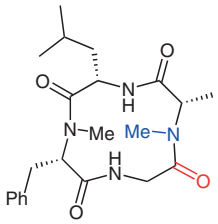
$ClCO_2i$-Pr (3 equiv)
$Me_2NBn$ (3 equiv)
DIEA (2 equiv)
MeCN–$H_2O$ (3.3 mM)
60 °C, 30 s




- $R^1$ = Me, $R^2$ = OBn (protected stellarin G) 87% yield
- $R^1$ = 3-indolyl, $R^2$ = H, 86% yield




74% yield




(dihydrotentoxin), 50% yield

**Significance:** Cyclic peptides are one of the most useful compounds as drugs. Although these compounds are generally synthesized by head-to-tail cyclization, the use of an excess amount of expensive coupling reagents and long reaction times are problematic. The authors have revealed that the acylammonium species generated from inexpensive tertiary amine and alkylchloroformate is an efficient coupling reagent for this approach.

**Comment:** Acylammonium species selectively react with C-terminal carboxylate by ionic interaction to give the active anhydride. Subsequently, head-to-tail cyclization occurs smoothly at the C-terminal anhydride with N-terminal amine. This method dramatically improved the efficiency of reactivity compared with traditional pathways to synthesize penta- and tetra-peptides.

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Synfacts 2023, 19(08), 0837 Published online: 14.07.2023
**DOI:** 10.1055/s-0042-1752862; **Reg-No.:** H06923SF



**Category**
Peptide Chemistry

**Key words**
cyclization
specialty peptides
natural products
continuous flow
acylammonium

Synfact of the Month