Experimental 4 Laboratory Report

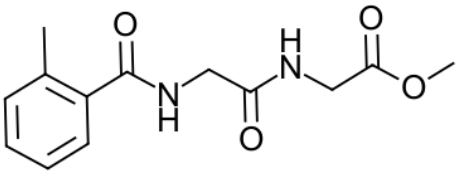
Results

Table 1. Reagents used in the synthesis of a dipeptide derivative.

Reagent	Molar mass (g/mol)	Mass used (g)	Volume (mL)	Millimoles	Intended mol ratio
2-methyl hippuric acid	193.1988	1.7948	-	9.29	1
Methyl glycinate hydrochloride	125.55	1.1722	-	9.34	1
Dichloromethane	84.93	-	39	-	-
Triethylamine	101.19	-	2.2	-	-
1M Dicyclohexyl-carbodiimide	206.333	-	9.29	9.29	1
Acetic acid	60.052	-	0.5	-	-
5% Hydrochloric acid	36.46	-	20	-	-
5% Sodium bicarbonate	84.007	-	20	-	-
Sodium sulfate	142.04	< 5	-	-	-
Ethanol	46.068	-	~8	-	-
Petroleum Ether	-	-	~16	-	-

Product information

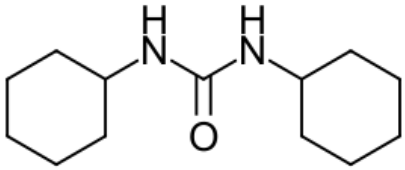
Desired product

Name (IUPAC)	Methyl {[(*o*-toluoylamino)methyl]carbonylamino}acetate
Structure	
Formula	$C_{13}H_{16}N_2O_4$
Molar mass	264.2767 g/mol
Literature melting point	215°C*
Experimental melting point	90 - 91°C
Theoretical yield	2.4551 g
Experimental yield	0.3323 g
Percent yield	13.5%

*This melting point is for a similar compound, glycylglycine.

National Center for Biotechnology Information (2024). PubChem Compound Summary for CID 11163, Glycylglycine. Retrieved October 23, 2024 from https://pubchem.ncbi.nlm.nih.gov/compound/Glycylglycine.

Byproduct

Name	Dicyclohexylurea (DCU)
Structure	
Formula	$C_{13}H_{24}N_2O$
Molar mass	224.34 g/mol
Literature melting point	-
Experimental melting point	-
Theoretical yield	2.084 g
Experimental yield	-
Percent yield	-

Calculations

mmols 2-methylhippuric acid = $1.7948\ g \times \frac{1000\ mmol}{193.1988\ g} = 9.29\ mmols$

mmols Methyl glycinate hydrochloride = $1.1722\ g \times \frac{1000\ mmols}{125.55\ g} = 9.34\ mmols$

mmols DCC = $9.29\ mL\ of\ 1M = 9.29\ mmols$

Limiting reagent

9.29 < 9.34

Either 2-methylhippuric acid or DCC can be used as the limiting reagent

1 mol reagents → 1 mol product

Theoretical yield

9.29 mmols product $\times \frac{264.2767\ g}{1000\ mmol} = 2.4551\ g$

Percent yield

$$= \frac{0.3233\ g}{2.4551\ g} \times 100\% = 13.5\%\ yield$$

The experimental melting point for the product was 90 - 91°C. No literature melting point for the exact product was found so the melting point of a similar compound, the dipeptide glycylglycine, was retrieved instead. This melting point is 215°C, meaning the experimental melting point is significantly depressed compared to glycylglycine's. However the experimental melting point is a tight range, and while the major difference in temperature does not support the identity of the product, the narrow range could suggest a fairly pure product.

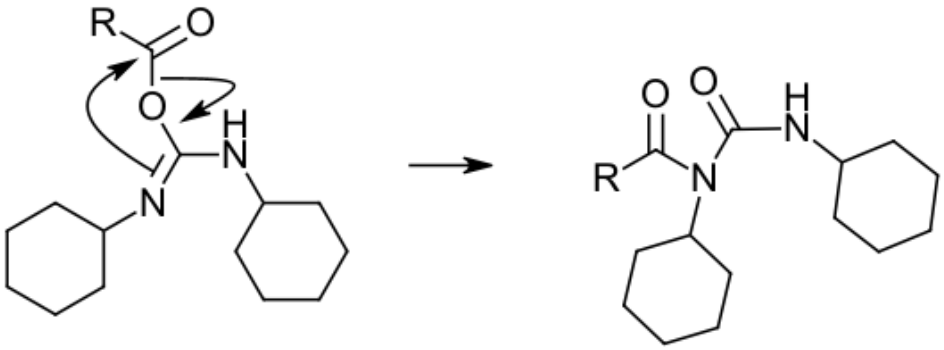
The yield of this synthesis was 0.3233 g or 13.5%, which is relatively low. Multiple factors could have contributed to low yield including not keeping ideal reaction temperature, or poor product isolation procedure.

The unknown acid chloride which was used in the experiment 3 synthesis is present in this experiment's product as the terminal toluoyl group. The identity of the acid chloride used is o-tolouyl chloride and the aromatic region of the ^{1}H NMR spectrum of both the experiment 3 product and the experiment 4 product can support this identification. For the experiment 4 product, it appears that the solvent peak is interfering with the aromatic region and the precise splitting pattern is indeterminable.

Discussion

Since the formation of an N-acylurea byproduct is likely an intramolecular process, or that it likely is a process requiring higher activation energy than the desired mechanism, keeping temperatures moderate would decrease the amount of N-acylurea forming reactions which occur.

A possible mechanism for this byproduct formation is presented below, and would occur after completion of step 2 in the desired mechanism.



Mechanism Step 2 Product

N-acylurea byproduct

Triethylamine was also added to the reaction mixture in one equivalent to the other reagents. Triethylamine is usually used as a moderate to strong base, and it is necessary in the reaction mixture to deprotonate the methyl glycinate starting material. This is a cation which comes in with a chloride counter ion. The triethylamine deprotonates the nitrogen atom to an R-NH_2 and greatly increasing its nucleophilicity so that it can attach the electrophilic carbonyl carbon in mechanism step 3. One equivalent is necessary so that it is less likely the triethylamine deprotonates other molecules like the carboxylic acid starting material or intermediates.

Mechanism

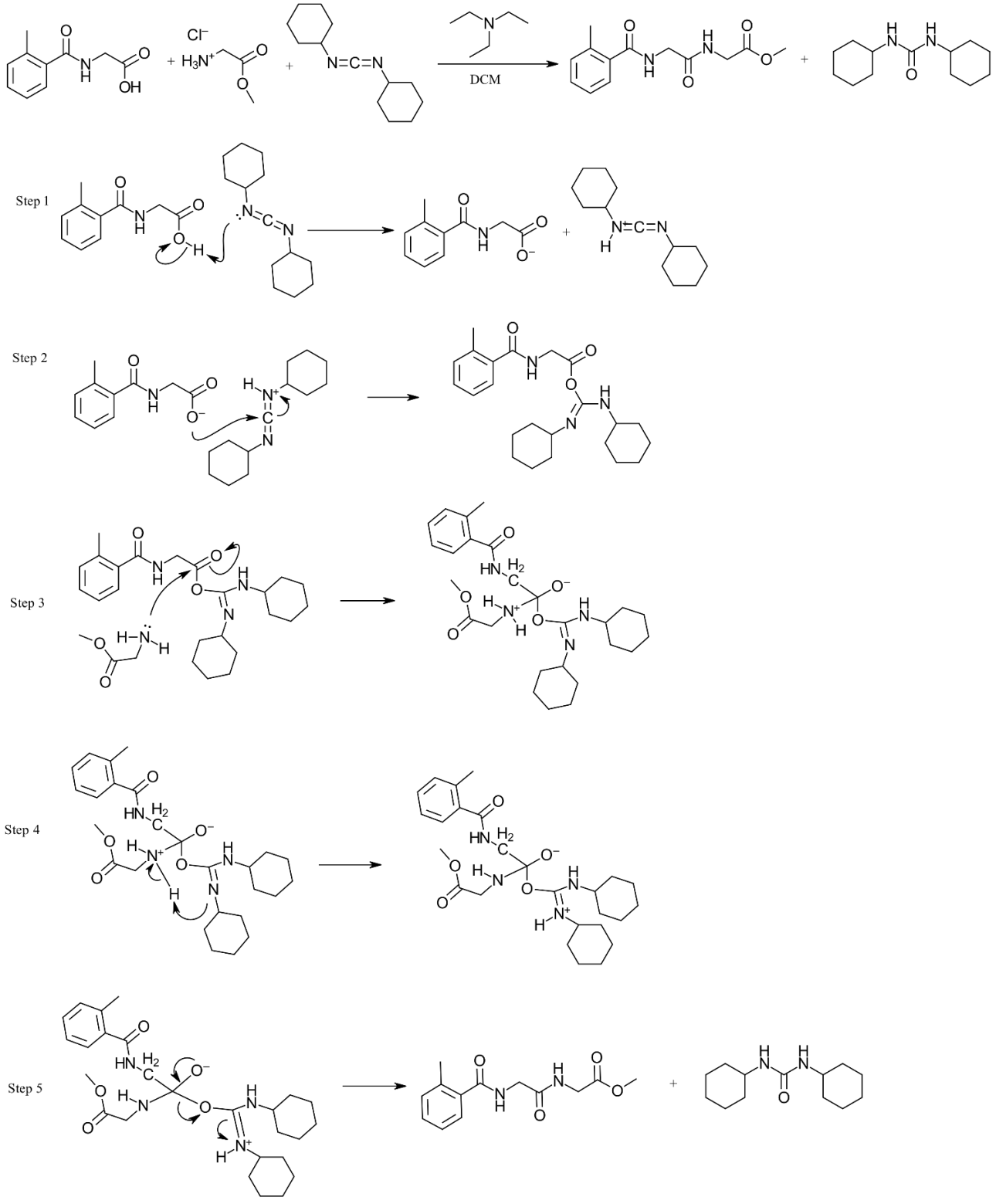


Figure 1. Proposed mechanism of the formation of a glycine dipeptide derivative from 2-methyl hippuric acid and methyl glycinate hydrochloride in the presence of DCC.

The first step of this mechanism is one of DCC's nitrogens deprotonating the carboxylic acid of the 2-methyl hippuric acid starting material. The second step is the carboxylate anion attacking the electrophilic sp hybridized central carbon of protonated DCC. This forms a neutral intermediate molecule. The next step happens when the nucleophilic nitrogen of methyl glycinate hydrochloride starting material attacks the electrophilic carbonyl carbon of the DCC/SM intermediate. The product is a neutral intermediate with separated charges. Step four is a proton transfer step where the positive nitrogen that just attacked loses a proton, and the sp^2 nitrogen of DCC gains a proton. The final step happens when the negatively charged oxygen (attackee in step three) donates electrons to form a C=O, and then electrons move to break the bond between newly formed product and what began as DCC. This forms the desired product and DCU as a byproduct.