An Easy Synthesis of Diazoacetamides.

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Abstract: Diazoacetamides of amino acids were synthesized via the coupling of an amine with the tosylhydrazone of glyoxylic acid followed by treatment with triethylamine.

As part of a programme directed towards the synthesis of enzyme inhibitors¹, we needed an efficient way to achieve the following reaction:

$$RNH_2 \longrightarrow RNH-CO-CHN_2$$

This is usually accomplished² by coupling an amine with the acid function of the glycine residue followed by diazotization of the glycyl derivative in aqueous acid. If this method is satisfactory when the product is soluble in organic solvent (e. g. dichloromethane) it is specially inappropriate to derivatize poorly soluble peptides.

We tried therefore to extend to amines the method of Blankley et al^3 which involves the reaction of glyoxylic acid chloride p-toluenesulfonylhydrazone in the presence of triethylamine. Despite the ameliorations brought to this method⁴, the problems associated with the obtention of the acid chloride of 2 prompted us to take advantage of the coupling methodology of peptide chemistry previously used in the obtention of diazoacetic ester of 3-hydroxy retinal⁵. Table 1 summarizes the representative results.



The selected amine reacted smoothly with glyoxylic acid tosylhydrazone to afford 3 in moderate yield. The stability of 3 to acidic conditions (neat trifluoroacetic acid) will be extremely useful in diazoacetylation of polyaminated compounds as exemplified by the synthesis of mono diazoacetylated lysine. For insoluble compounds such as peptides, dimethylformamide was substituted to tetrahydrofuran⁷.

RNH ₂	3, Yield (%)	4, Yield (%)	1a, Yield (%)	1b, Yield (%)
Boc-Phe(p-NH2)-OMe	48	96	80	75
H-NorLeu-OMe	30	-	75 ^{1a}	-
H-Phe-OBz	45	- '	95	-
Boc-Lys-OMe	25	64	-	47
H-Lys(Boc)-OMe	35	64	-	50

Table 1: Yields⁶ in Isolated Compounds 3, 4, 1a & 1b.

This method which is the first report of diazoacetylation of an amine derivative using DCC can be advantageously compared to the recently described method using N_2O_4 in non polar aprotic solvent^{2d}.

The following procedure is typical for the preparation of 3. To a solution of 1 mmole of the free amine and 1.1 mmole of the hydrazone 2 in 10 ml of ice cold THF was added, dropwise, 1.1 mmole of DCC in 5 ml of THF. The mixture was allowed to warm to room temperature and stirring was continued for four hours. The DCU was filtered off and the product was purified by HPLC (C_{18} , Eluent: water and acetonitrile both with 0.05% trifluoroacetic acid).

Compound 4 was obtained by treating a solution of 1 mmole of 3 in 4 ml of acetonitrile with 1 ml of trifluoroacetic acid at room temperature for two hours. The product was purified by HPLC (C_{18} , same eluent as above).

For the generation of a diazoacetyl group, 1 mmole of compound 3 or 4 in 5 ml of acetonitrile was treated with 2 mmoles of triethylamine at room temperature for one hour. The diazocompounds were purified by HPLC (C_{18} , Eluent: water and acetonitrile, no acid !).

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REFERENCES AND NOTES

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- 6. All the compounds were isolated and characterized by ¹H, ¹³C NMR; when possible they were characterized by mass spectrometry, IR and microanalysis. Given yields correspond to a single step.
- One molar equivalent of 1-hydroxybenzotriazole was required to avoid the formation of the dimethylformamidino derivative (RN=CH-N(CH₃)₂) of the starting amine. Derivatisation of peptides will be reported elsewhere.

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