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Communications

A New Diazoacylating Reagent: Preparation, Structure, and Use of Succinimidyl Diazoacetate

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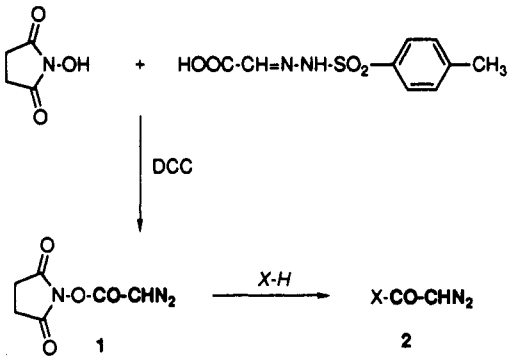
Summary: The easily obtained and very stable title compound 1 can be used for direct diazoacetylation of aromatic or aliphatic amines, phenols, thiophenol, and peptides under mild conditions.

Diazoacetylation classically proceeds in two steps through the glycyl derivative.[1] Despite extensive improvements in this field[2,3] only a few methods have been concerned with the synthesis of diazoacetamides. The recent diazotization in nonpolar aprotic solvent using N_2O_4 at low temperature[4a] as well as the cyclohexylcarbodiimide-mediated coupling of an amine with glyoxylic acid tosylhydrazone[4b] considerably improved the synthetic routes of diazoacetamides. The wide range of application of diazocarbonyl compounds in chemistry[5] as well as in biochemistry[2,6] justifies the development of new diazoacylating agents.

We wish to report here the synthesis and the potential applications of a new compound allowing diazoacetylation of amines and other nucleophiles in a single step, succinimidyl diazoacetate 1. This compound was easily



obtained[7] by the reaction of *N*-hydroxysuccinimide with glyoxylic acid tosylhydrazone[3d] in the presence of dicyclohexylcarbodiimide. The formation of 1, the mechanism of which is under investigation, occurred spontaneously in the reaction medium since no trace of succinimidyl glyoxylate tosylhydrazone could be detected. The high stability of crystalline compound 1, in contrast to the reported unstability of the corresponding acid chloride,[3c] allows its unlimited storage at room temperature without decomposition.

The molecular shape, as given by the X-ray analysis,[8] confirms the cis conformation of the carbonyl and the CNN group and the atomic distribution in the two nearly (85°) perpendicular planes of succinimidyl and diazoacetyl groups. No special structural feature can explain the enhanced stability of compound 1.

The reaction of diazoacetylation of amines with 1 could

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be carried out from neutral to basic conditions.[11] This represents a great improvement over previous syntheses of acid-sensitive diazoacetyl compounds and can be advantageously compared to most of the previously reported methods using acidic to neutral conditions. Our preliminary results on amines are summarized in Table I. Besides its efficiency in derivatizing alkylamines (entries 1–4) or arylamine (entry 5), this reagent is especially useful in the functionalization of esterified α-amino acids (entries 6–9). Moreover, the totally regioselective acylation at the ω-amino group of α,ω diamino esters is of special interest (entry 9). As mentioned above, the synthetic applications of 1 are not restricted to amines. Aliphatic and aromatic thiols and alcohols are also proned to diazoacetylation in excellent yield under conditions (NaH/THF) which did not affect the stability of 1.

The scope of applications of succinimidyl diazoacetate in chemistry and enzymology is currently explored.

Table I. Yields in Purified Diazoacetylated Compounds 2

entry	XH	rctn condns[11]	2 yield (%)
1	heptylamine	method A, 1 h	93
2	hexadecylamine	method A, 1 h	84
3	piperidine	method A, 1 h	98[12]
4	morpholine	method A, 1 h	97
5	*p*-methoxyaniline	method B, 12 h	60
6	H-Nle-OMe	method B, 4 h	64[6b]
7	H-Phe-OBz	method B, 4 h	60
8	H-Pro-OBg[14]	method C, 12 h	59
9	H-Lys-OMe	method C, 1 h	30
10	H-Pro-Ile-Val-NH_2	method B, 1 h	30
11	H-Tyr-Pro-Leu-Gly-NH_2	method C, 12 h	35
12	2-naphthol	method D, 15 min	95
13	phenol	method D, 15 min	90[3c,13]
14	thiophenol	method D, 15 min	70[3c]

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Supplementary Material Available: Characterization data for compound 2 (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(7) To a solution of 1.15 g (10 mmoles) of *N*-hydroxysuccinimide and 2.42 g (10 mmoles) of glyoxylic acid tosylhydrazone[3d] in 100 mL of ice-cold dioxane was added, dropwise, a solution of 2.06 g (10 mmol) of DCC in 20 mL of dioxane. The mixture was allowed to warm to room temperature, and stirring was continued for 4 h. DCU was filtered off, and the filtrate was evaporated to dryness in vacuo. The product was purified by chromatography on silica gel with dichloromethane as eluent to give 1.18 g (65%) of 1. Mp: 119–120 °C. ^{1}H NMR ($CDCl_3$ 200 MHz): δ 2.85 (s, 4 H, CH_2(succinimide)), 5.13 (s, 1 H, CHN_2). ^{13}C NMR: δ 25.40 (CH_2(succinimide)), 45.03 (CH_2(succinimide), 162 (CO(diazoacetyl)), 169.3 (CO(succinimide)). Mass spectrometry; (electronic impact) *m/z* 184 (21, M + 1), 156 (42, (M + 1 − N_2), 69 (100, $COCHN_2$); (chemical ionization, NH_3) *m/z* 201 (100, M + NH_4). IR ($CHCl_3$): 2100 cm^{-1} diazo group. Anal. Calcd for $C_6H_5N_3O_4$: C, 39.34; H, 2.73; N, 22.95; O, 34.97. Found: C, 39.59; H, 2.8; N, 22.98; O, 35.1.

(8) **Crystal Structure Analysis.** A crystal of about 0.6 × 0.5 × 0.2 mm^3 was mounted on a graphite-monochromated Nonius CAD4 diffractometer using the Cu Kα wavelength (λ = 1.5418 Å.). Three standards measured every 3 h, no decay. Space group $P2_12_12_1$, *a* = 6.679(10) Å, *b* = 8.238(8) Å, and *c* = 14.51(2) Å. Lorentz and polarization corrections, no absorption (μ = 1.1 cm^{-1}). 2919 measured reflections (−8 < *h* < 8, −9 < *k* < 9, 0 < *l* < 17), from which 869 independent and 847 used [$I > 3\sigma(I)$]. Structure solution using direct methods[9] and refinement by the full-matrix least-squares method.[10] Hydrogen atoms localized on difference-series. Anisotropic thermal parameters for C,N,O atoms, isotropic for H atoms. Final discrepancy factors $R = 5.2$ and $R_w = 4.8$, weights $w = [\sigma^2(F) + 0.0005F^2]^{-1}$, σ from counting statistics. C=O bond length: 1.208(3) Å.

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(11) Preparation of **2**. **Method A.** The amine (20 mmol) in 5 mL of THF was treated, as room temperature, by 10 mmol of **1**. The solvent was evaporated in vacuo, and the product was purified by chromatography on silica gel. **Method B.** The amine (10 mmol) in 5 mL of DMF was treated, at 60 °C, by 10 mmol of **1**. The product was purified by HPLC (C_{18}, water and acetonitrile as eluents). **Method C.** Same as in method B but the reaction is carried out at room temperature. **Method D.** 2 mmol of the starting product in 5 mL of dry THF was added dropwise to a suspension of NaH (100 mg, 60% dispersion in oil) in 5 mL of dry THF. 2 mmol of succinimidyl diazoacetate in 5 mL of THF was added, and stirring was continued for 10 min. The precipitate formed was filtered off, and the final product was purified by chromatography on silica gel.

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