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3-(5-NITRO-2-PYRIDON-1-YL)-1,2-BENZOISOTHIAZOLE 1,1-DIOXIDE (BID-NPy) AS A NEW EFFECTIVE CONDENSING REAGENT

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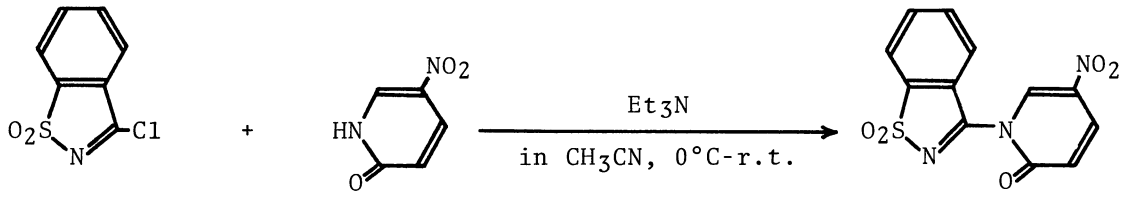
3-(5-Nitro-2-pyridon-1-yl)-1,2-benzoisothiazole 1,1-dioxide (BID-NPy) was found to be a useful condensing reagent. Various dipeptides and esters were prepared in good yields using this reagent.

In the previous paper,[1] we have reported that 3-(succinimidoxy)-1,2-benzoisothiazole 1,1-dioxide (BID-OSu) is a useful condensing reagent for peptide synthesis. In continuation to our study on the development of a new condensing reagent,[1,2] we tried to prepare various saccharin derivatives which are generally stable crystalline compounds and found that 3-(5-nitro-2-pyridon-1-yl)-1,2-benzoisothiazole 1,1-dioxide (BID-NPy) was a new condensing reagent for the preparation of esters and peptides.

BID-NPy was prepared as follows: to a mixed suspension of 3-chloro-1,2-benzoisothiazole 1,1-dioxide[3] (I, 2.02 g, 10 mmol) and 5-nitro-2-pyridone (II, 1.121 g, 8 mmol) in dry acetonitrile (25 ml) was added triethylamine (0.81 g, 8 mmol) at 0°C. A yellowish white crystalline precipitate started to separate almost immediately. After stirring for about 2 h at room temperature the precipitate was filtered off, washed with chloroform to remove triethylammonium chloride and recrystallized from acetonitrile to give pure BID-NPy in 77% yield (1.89 g, mp 239-241°C). The structure of BID-NPy was confirmed by elemental analysis (Found: C, 47.24; H, 2.18; N, 13.54%. Calcd for $C_{12}H_7N_3O_5S$: C, 47.22; H, 2.31; N, 13.77%) and IR spectrum, which clearly shows the presence of the carbonyl group at 1670 cm^{-1}. This compound was quite stable on storage, whereas I was very unstable.



I II BID-NPy, 77%

Table 1. Preparation of Esters

$$\text{BID-NPy} + R^1COOH + R^2OH \xrightarrow[\text{-10°C to r.t. overnight}]{Et_3N \text{ in } CH_2Cl_2} R^1COOR^2$$

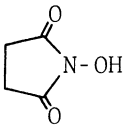
R^1CO_2H	R^2OH	Yield (%)	$\nu C{=}O$ (cm^{-1})
$PhCH{=}CHCO_2H$	$PhCH_2OH$	92	1710
$PhCH_2CO_2H$	$PhCH_2OH$	95	1735
$PhCH_2CO_2H$	$O_2NC_6H_4OH$	96	1760
$PhCH_2CO_2H$	CCl_3CH_2OH	93	1735
$PhCO_2H$	C_6Cl_5OH	93	1745
$PhCO_2H$	$O_2NC_6H_4OH$	88	1735
$PhCO_2H$		93	1765, 1735

Table 2. Preparation of Protected Dipeptide Esters

$$\text{BID-NPy} + \text{Y-A.A.-OH}^{a)} + Et_3N \xrightarrow[\text{in } CH_2Cl_2]{\text{-10°C to 0°C, 2h}} \xrightarrow[\text{r.t. overnight}]{\text{H-A.A.-OR}} \text{Y-dipeptide-OR}$$

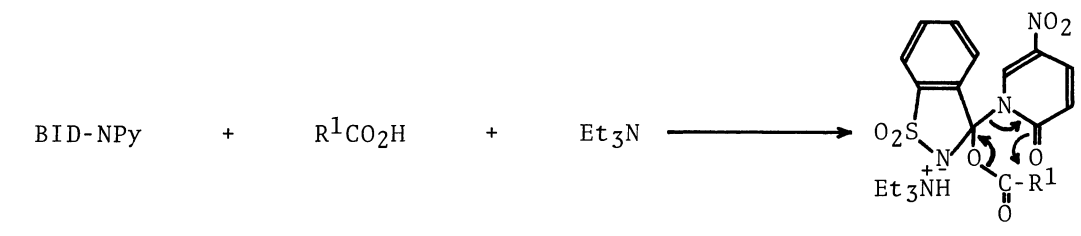
Product	Yield (%)	Mp (°C) (lit)[4]	$[\alpha]_D$(c, solv) (lit)[4]
Z-Val-Gly-OEt	86	163-164 (162-164)	-27.0 (0.77, EtOH) (-27.0)
Z-Ala-Gly-OEt	87	98-99 (99-100)	-21.8 (3.60, EtOH) (-22.2)
Z-Met-Gly-OEt	85	94-95 (94-96)	-19.6 (3.50, EtOH) (-19.8)
Z-Cys(Bzl)-Gly-OEt	quant.	97-98 (97-99)	-28.6 (5.86, AcOEt) (-27.0)
Boc-Phe-Val-OMe	84	115-117 (118-119)	-11.2 (1.99, DMF) (-11.6)
Boc-Leu-Leu-OMe	73	134-135 (132-133)	-50.2 (0.41, MeOH) (-50.4)
Boc-Ala-Val-OMe	85	66-67 (63-64)	-49.4 (0.36, MeOH) (-49.5)
Boc-Leu-Val-OMe	83	143-145 (144-147)	-41.0 (0.52, MeOH) (-41.1)

a) This means N-protected amino acids (Y = Z or Boc).

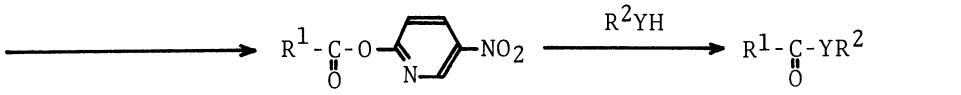
BID-NPy thus prepared was allowed to react with carboxylic acid in order to check its reactivity as follows: to a mixed suspension of BID-NPy (152 mg, 0.5 mmol), phenyl acetic acid (68 mg, 0.5 mmol) and benzyl alcohol (54 mg, 0.5 mmol) in dichloromethane (3 ml) was added a solution of triethylamine (51 mg, 0.5 mmol) in dichloromethane (2 ml) at -10°C under N_2. The suspension became clear after a few minutes because of consumption of slightly soluble BID-NPy in the progress of the reaction. The reaction temperature was gradually raised to room temperature. After stirring overnight, the solvent was evaporated in vacuo and the resulting residue was taken up in 30 ml of ethyl acetate. This was then successively washed with saturated solution of $NaHCO_3$, 1 mol dm^{-3} HCl, and a saturated solution of NaCl, dried over anhydrous Na_2SO_4, and evaporated to dryness in vacuo. The resulting residue was subjected to preparative TLC (silica gel, ethyl acetate/benzene, 1/5, v/v) to give benzyl phenylacetate in 95% yield (112 mg). In a similar manner, various esters were prepared in excellent yields as shown in Table I.

This versatile reagent, BID-NPy, also proved to be an excellent reagent for synthesizing various protected dipeptide esters, the results of which are shown in Table 2. The following description is illustrative of the experimental procedure for the preparation of dipeptide esters: to a mixed suspension of BID-NPy (152 mg, 0.5 mmol) and Z-Cys(Bzl)-OH (173 mg, 0.5 mmol) in dichloromethane (3 ml) was added a solution of triethylamine (51 mg, 0.5 mmol) in dichloromethane (2 ml) dropwise at -10°C under N_2. After stirring for 2 h at -10 to 0°C, H-Gly-OEt·HCl (70 mg, 0.5 mmol) was added to the reaction mixture, followed by the addition of triethylamine (51 mg, 0.5 mmol) in dichloromethane (2 ml). The solution was stirred at 0°C for 2 h, and kept stirring overnight at room temperature. The reaction mixture was worked up similarly as that of the preceding example and evaporated to dryness in vacuo. The resulting residue was subjected to preparative TLC using silica gel as stationary phase and benzene/ethyl acetate (1/1, v/v) as solvent to afford the desired product. Recrystallization from benzene-hexane gave the pure product, Z-Cys(Bzl)-Gly-OEt in quantitative yield (208 mg). In a similar procedure, various dipeptide esters were obtained (Table 2).

The probable course of the reactions of BID-NPy with acids is illustrated in the following scheme:



III



IV V (Y=O, N, S[5])

Formation of the activated ester (IV) through a cyclic transition state (III) presumably is followed by the attack of the nucleophile (R^2YH) to give the product (V). In support of this mechanism, the activated ester (IV, R^1 = $PhCH_2$), an unstable crystalline compound [IR νC=O at 1755 cm^{-1}, NMR ($CDCl_3$) δ 3.91 (s, 2H), 7.17 (d, 1H, J=9Hz), 7.28 (s, 5H), 8.40 (d×d, 1H, J=3Hz, 9Hz), 9.10 (d, 1H, J=3Hz)], was isolated from the reaction mixture prior to the addition of nucleophile (R^2YH) by short silica gel column chromatography using chloroform as eluting solvent.

Thus, the characteristics and the effectiveness of BID-NPy is apparent from the following: 1) this reagent, being a stable crystalline compound, can be easily prepared from an inexpensive industrial product, saccharin, 2) it is effective in the preparation of both esters and peptides of wide range, and 3) the reaction conditions are mild and yields are also high.

Further investigation is being continued for elucidating the scope and the limitation of the reagent in the synthesis of macrolides and polypeptides.

REFERENCES AND NOTES

1) K. Inomata, H. Kinoshita, H. Fukuda, O. Miyano, Y. Yamashiro, and H. Kotake, Chem. Lett., 1979, 1265.

2) H. Kinoshita, K. Inomata, O. Miyano, and H. Kotake, Bull. Chem. Soc. Jpn., 52, 2619 (1979).

3) The compound I (BID-Cl) was prepared in 76% yield by the following improved method[6]: a mixture of $SOCl_2$ (10.62 g, 90 mmol) and saccharin (5.496 g, 30 mmol) was refluxed for 15 h in xylene (100 ml) in the presence of 0.8 g of active charcoal and a catalytic amount of dimethyl formamide (0.19 g, 2.6 mmol). After filtration and evaporation of the solvent in vacuo, the resulting product was recrystallized from dry benzene.

4) References cited in 1 and 2.

5) S-(4-Methylphenyl) thiobenzoate (V, R^1 = Ph, R^2 = p-$CH_3C_6H_4$) was also prepared in 93% yield.

6) M. Wataya, M. Yamaguchi, and N. Onodera, Japan. Kokai 75 24,271; Chem. Abstr., 83, 147471b (1975).

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