Tetrahedron Letters No. 6, pp 555 - 558.

0040-4039/79/0201-0555$02.00/0

THE USE OF 2-NITROPHENYLPROPIONIC ACID AS A PROTECTING GROUP FOR AMINO AND HYDROXYL FUNCTIONS TO BE RECOVERED BY HYDROGEN TRANSFER REDUCTION

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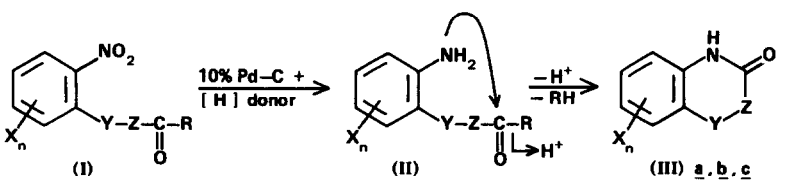
We have demonstrated the potential in a peptide sequencing procedure for the use of hydrogen transfer reduction of 2,6-dinitrophenyl derivatives[1] of amino acids and peptides using the sequence (I)→(III), e.g. for (Ia) where R = peptide or amino acid residue. For the compounds (Ia) where R is an amino or hydroxyl function this sequence was considered as a



(I) (II) (III) a.b.c

a X_n = 6–NO_2, Y= NH, Z = $CH(CH_3)$

b X_n = H, Y = Z = CH_2, R = OH

c X_n = H, Y–Z = (CH=CH), R=OH

$H_2N-(CH_2)_xCONHCH_3$

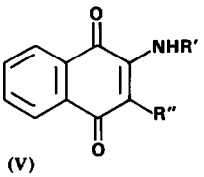
(IV)

potential method for removal of a protecting group. Using our reported conditions[2,3] for transfer hydrogenation of nitroaryl compounds, cleavage of amides and esters of the acid (Ia), R=OH was readily achieved. However, it was considered more pertinent to investigate general application of the sequence (I)→(III) using a more stable and less complex acid than (Ia) as a protecting group.

The reported pseudounimolecular rate constants for base-catalysed lactam formation from amino-amides[4] (IV) indicate that ring formation occurs most readily for x=4 suggesting that the sequence (II)→(III) should occur readily for an acid where Y=Z=CH_2. As previous work had shown that mononitroaryl compounds were readily reduced to anilines by hydrogen transfer using either cyclohexene[2] or sodium phosphinate[3] with 10% Pd-C as catalyst, 2-nitrophenylpropionic acid[5] (Ib) and its derivatives were expected to undergo

sequence (I)→(III) readily. Indeed reduction of (Ib) to 2-aminophenylpropionic acid and its spontaneous cyclisation to the lactam [(IIIb), hydrocarbostyril][6] occurred rapidly. Simple alkylamides and esters of (Ib) behaved similarly.

The more complex derivatives (1)→(7) obtained from either the acid chloride or anhydride of (Ib) were subsequently reduced rapidly in high yield using the donors listed (D and E). Examples (1)→(3) illustrate situations where an alternative deprotection by hydrolysis could result in mixed amino products. Cleavage of (4) to yield the N-methylamide of DL-α-alanine demonstrates the use of 2-nitrophenylpropionic acid as an amino acid or peptide protecting group. Transfer hydrogenation using cyclohexene as hydrogen donor has been reported to effect deprotection of benzyloxycarbonyl[7] derivatives of amino acids. The use as a general protecting group removable by transfer hydrogenation with sodium phosphinate is now demonstrated by examples (8), (9) and (10). Benzyl chloroformate does not react with the weakly nucleophilic 2-amino-3-chloro-1,4-naphthoquinone (Va) but the anhydride of (Ib)



(V)

a R' = H, R'' = Cl
b R' = A, R'' = Cl
c R' = A, R'' = NHC_8H_{17}
d R' = H, R'' = NHC_8H_{17}

in admixture with concentrated H_2SO_4 readily yields the amide (Vb). Addition of octylamine to this activated quinone gives (7) which is readily reduced in the presence of air by hydrogen transfer. Heating the intermediate product in xylene at 80-100° effects the sequence (II)→(III) to yield (Vd). This sequence illustrates a preferred route to quinones of this type.[8,9]

Deprotection of the derivative (6) obtained by methylation of the anilide of (Ib) illustrates a potential use as an alternative to trifluoroacetylation in a valuable method for obtaining N-alkylanilines.[10]

Reported hydrogen transfer reductions of styrenes[11] suggested the similar possible use of the readily available trans 2-nitrocinnamic acid (Ic) as a protecting group. Full reduction in situ to the 2-aminophenylpropionyl group would allow sequence (II)→(III) to occur. Although in this study the lactam (IIIb) was slowly formed from the free acid utilising cyclohexene as hydrogen donor, it was not formed using sodium phosphinate as donor. The very slow reduction of the olefinic bonds in (13) and (14) discourages the utility of protection with (Ic), since, not unexpectedly, the readily obtained intermediate trans-2-aminocinnamoyl derivatives do not cyclise to the lactam (IIIc).

The results in the Table serve therefore to demonstrate that where the removal of protecting groups from amino and some hydroxyl functions needs to be carried out under non-hydrolytic conditions or without the use of gaseous H_2, catalytic hydrogen transfer

reductions using donors such as cyclohexene or sodium phosphinate offer a rapid mild procedure.

Table 1

Catalytic transfer hydrogenolysis of amino and hydroxy compounds protected by 2-nitrophenylpropionyl (A), benzyloxycarbonyl (B) and 2-nitrocinnamoyl (C)

No.	Amide or ester[a]	m.p.°C	[H] donors D[2], E[3]	Reaction time (min) (d)	% Deprotection (b)
(1)	3-ANH-quinoline	105-106	D	30	90
			E	15	95
(2)	3,4-Cl_2-C_6H_3NHA	127-128	D	60	90
			E	60	80 (90c)
(3)	4-ANH-C_6H_4-$CH(COOC_2H_5)_2$	98-99	D	60	85
			E	30	90
(4)	ANH-$CH(CH_3)CONHCH_3$(DL)	175-176	D	20	85(d)
			E	30	75(d)
(5)	2-AO-naphthalene	81-82	E	30	90
(6)	AN(CH_3)-C_6H_5	63-64	E	35	85
(7)	2-ANH-, 3-C_8H_{17}NH-1,4-naphthoquinone	129-130	E	30	90
(8)	2-BO-naphthalene	70-71	E	45	81
(9)	3,4-$Cl_2C_6H_4$NHB	120-121	E	60	75
(10)	5-BNH-quinoline	155-156	D	15	85
			E	25	80
(11)	2-nitrophenylpropionic acid		E	15	ca 100
(12)	2-nitrocinnamic acid[e]		D	300	60
			E	300	0
(13)	3-CNH-quinoline	203-204	D	420	10
			E	300	0
(14)	4-CNH-$C_6H_4CH_2(COOC_2H_5)_2$	154-156	D	250	15

(a) Satisfactory elemental analysis and spectral data obtained to support identity

(b) Based on recovery of amine or alcohol

(c) Reduction product heated

(d) Reaction terminated when t.l.c. indicated amides or ester no longer present. D=cyclohexene, E=NaH_2PO_2

(e) Commercially available

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(Received in UK 4 December 1978)