A Simple One-step Synthesis of *N*-Substituted Isoindolin-1-ones. Diastereofacially Selective Protonation of an Intermediate Isoindolinol

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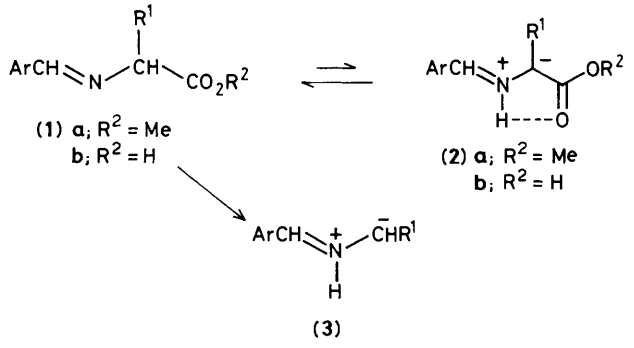
α-Amino acids and their methyl esters, arylamines, heterocyclic amines and, less efficiently, aryl substituted aliphatic amines, react with *o*-phthaldialdehyde in the presence of acetic acid to give *N*-substituted isoindolin-1-ones in excellent yield; deuteriation studies implicate an isoindolinol intermediate and, when α-amino acids are used, provide evidence of its diastereofacially selective protonation.

We have reported the facile and stereospecific generation of azomethine ylides from imines of α-amino acid esters by a formal 1,2-prototropic shift, (**1a**) ⇌ (**2a**).[1] Free α-amino acids also react with aryl aldehydes to generate the analogous dipole, (**1b**) ⇌ (**2b**), in acetic acid[2] whilst in other solvents [dimethylformamide (DMF), MeOH, or MeCN] decarboxylation occurs generating a new dipole (**3**).[3] In extending this work we investigated the reaction of *o*-phthaldialdehyde (**4**) with α-amino acids in boiling acetic acid (non-decarboxylating conditions). Rapid reaction (5—10 min) occurred to give the *N*-substituted isoindolin-1-ones (**5a**—**f**) (Table 1) in good yield. The α-blocked amino acid (**6**) reacted similarly (Table 1) to give (**5g**). The reaction appears to be general (α-amino esters react similarly) and can be carried out in other solvents (MeCN, $CHCl_3$, or Et_2O) often at much lower temperatures (0—80 °C) with only a catalytic amount of acetic acid. Thus γ-aminobutyric acid gives (**7a**) (52%), whilst the arylamines (**8a**—**c**) give (**7b**—**d**) in 70—78% yield. Heterocyclic amines (**9**) and (**10**) react with (**4**) at 0 °C in ether or ether–acetonitrile containing a catalytic amount of acetic acid to give (**7e**) (82%) and (**7f**) (91%), respectively. Initial studies suggest the reaction is less efficient with aliphatic amines. Thus dopamine and (**4**) give (**11a**) (40%), whilst norepinephrine and (**4**) give (**11b**), (26%).

The isoindolin-1-ones (**7a**—**f**) are distinguished by a singlet for the ring methylene group in their n.m.r. spectra ($CDCl_3$ or [$^2H_5$]pyridine) at δ 4.65—6.65, whilst in the α-amino acid products (**5a**—**e**) this methylene group gives rise to the expected AB pattern since the protons are diastereotopic in this case, *e.g.* (**5d**), δ ([$^2H_5$]pyridine) 4.42 (d, 1H, CHN) and 5.58 (d, 1H, CHN), J_{gem} 16.9 Hz.

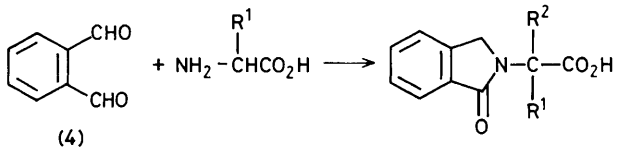
When the reaction of (**4**) and certain amines is carried out at low temperatures, and/or in the absence of acetic acid, intermediates of the expected type can be isolated. Thus (**12**) reacts (0.5% acetic acid in ether, 35 °C, 48 h) with (**4**) to give the monoimine (**13**) (72%) whilst phenylhydrazine and (**4**) (0.5% acetic acid in acetonitrile, 80 °C, 2 h) give (**14**) (65%) as bright yellow prisms, m.p. 120—121 °C. Secondary amines such as diethylamine and pyrrolidine react with *o*-phthaldialdehyde to give (**15a**) (71%) and (**15b**) (84%) respectively as



(1) a; R^2 = Me
b; R^2 = H

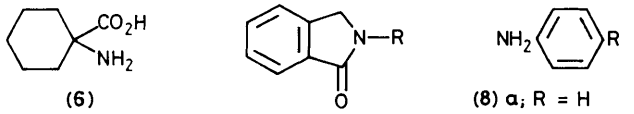
(2) a; R^2 = Me
b; R^2 = H

(3)



(4)

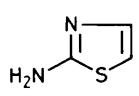
(5)



(6)

(7) a; R = $[CH_2]_3CO_2H$
b; R = Ph
c; R = C_6H_4OMe-*p*
d; R = C_6H_4COMe-*p*
e; R = 2-thiazolyl
f; R = 3-(5-methyl)isoxazolyl

(8) a; R = H
b; R = OMe
c; R = COMe



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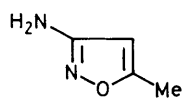
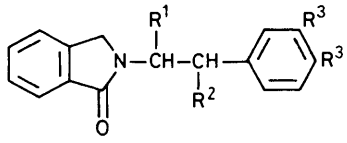
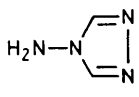


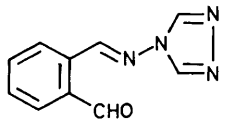
(10)



(11) a; R^1 = R^2 = H, R^3 = OH
b; R^1 = H, R^2 = R^3 = OH



(12)



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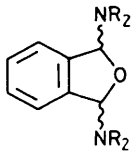
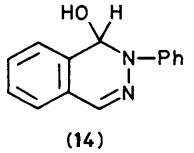


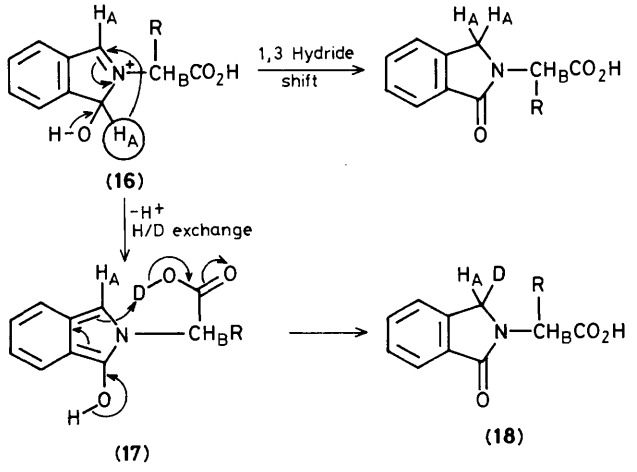
(15) a; R = Et
b; R_2 = $[CH_2]_4$



(14)

Table 1. Isoindolin-1-ones from α-amino acids and *o*-phthaldialdehyde.

α-Amino acid	Product (**5**), R^2 = H	Yield (%)
Valine	**a**; R^1 = Pr^i	80
Phenylalanine	**b**; R^1 = CH_2Ph	80
Serine	**c**; R^1 = CH_2OH	91
Alanine	**d**; R^1 = Me	60
Phenylglycine	**e**; R^1 = Ph	67
Glycine	**f**; R^1 = H	76
(**6**)	(**5g**, R^1R^2 = $-[CH_2]_5-$)	65



Scheme 1

thick yellow oils, the n.m.r. spectra ($CDCl_3$) of which show that they are mixtures of *cis*- and *trans*-isomers.

Thus (**16**) (Scheme 1) is a plausible intermediate and two mechanisms were considered for the formation of (**5**). A 1,3-hydride shift assisted by the hydroxy group of the hydroxy-iminium species (**16**, arrows)† or a deprotonation–reprotonation sequence *via* the isoindolinol (**17**) could both give rise to an isoindolin-1-one. We were also interested in the lability of H_B, the α-hydrogen atom of the original amino acid. When the reaction of *o*-phthaldialdehyde and α-amino acids was carried out in [$^2H_4$]acetic acid approximately one deuterium atom was incorporated into the $ArCH_2N$ group.‡ Less deuterium incorporation (*ca.* 34 *vs.* 70% $^2H_1$) occurred when, *e.g.*, alanine methyl ester was used in place of alanine

† It is recognised that the hydride shift could occur *via* a monohydroxyamine monoaldehyde intermediate.

‡ No [$^2H_2$]-species were detected but about 70% monodeuteriation occurred. [$^2H_0$]-Product arises owing to the competition from protons of water liberated during the reaction and to the use of undeuteriated amino acids.

Table 2. Diastereoisomer ratios of monodeuterio-(**18**).[a]

R in (**18**)	Ratio from (*S*)-amino acid	Ratio from (*R*)-amino acid
Alanyl	1:1.20	1:1.18
Phenylglycyl	1.22:1	1.22:1
Phenylalanyl	1.32:1	1.17:1
Valyl	1.63:1	2.05:1
Isoleucyl	2.30:1	2.03:1
$CH(Bu^t)CO_2H$	7.10:1	—

[a] *o*-Phthaldialdehyde (0.1 mmol) and the amino acid (0.1 mmol) were dissolved in [$^2H_4$]acetic acid (0.3 ml) (occasionally the sample had to be warmed to effect solution). [$^2H_6$]Benzene (0.3 ml) was added to assist spectral resolution and the n.m.r. spectrum was run after *ca.* 0.5 h. Ratios refer to the diastereoisomer with the lower δ value first.

suggesting the deuterium is delivered more efficiently *via* the intramolecular route (**17**, arrows) rather than intermolecularly. Diastereoface selectivity for the protonation step (**17**) → (**18**) is observed with one diastereoisomer predominating in all cases (Table 2). Both (*S*)- and (*R*)-amino acids give identical or very similar ratios of diastereoisomers (Table 2) as expected for intramolecular deuteron transfer *via* (**17**).§

The proton H_B (Scheme 1) is essentially non-labile under the reaction conditions as shown by lack of incorporation of deuterium at this site and by the slow racemisation of optically active (**5**, R^1 = Me, R^2 = H), $[\alpha]_D^{25}$ +8.8°, in glacial acetic acid ($[\alpha]_D^{25}$ +7.4° after 2.5 days at 25 °C).

Roth introduced the combination *o*-phthaldialdehyde and mercaptoethanol for the fluorimetric detection of α-amino acids.[4] The reagent is more sensitive than ninhydrin for α-amino acids and is used in borate buffer at pH 9.5. Subsequently it was shown that the species responsible for the fluorescence were isoindoles.[5] Our reactions are performed under acid catalysis in the absence of mercaptans and are thus diverted to the isoindolin-1-ones.

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References

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§ Assuming deuteron transfer occurs to the face remote from R in (**17**), then (*S*)-amino acids should give the (*R*)-configuration, and (*R*)-amino acids the (*S*)-configuration, at the new chiral centre in monodeuterio-(**18**).