Reactions of Some 1,3-Diaminonucleophiles with Azlactones

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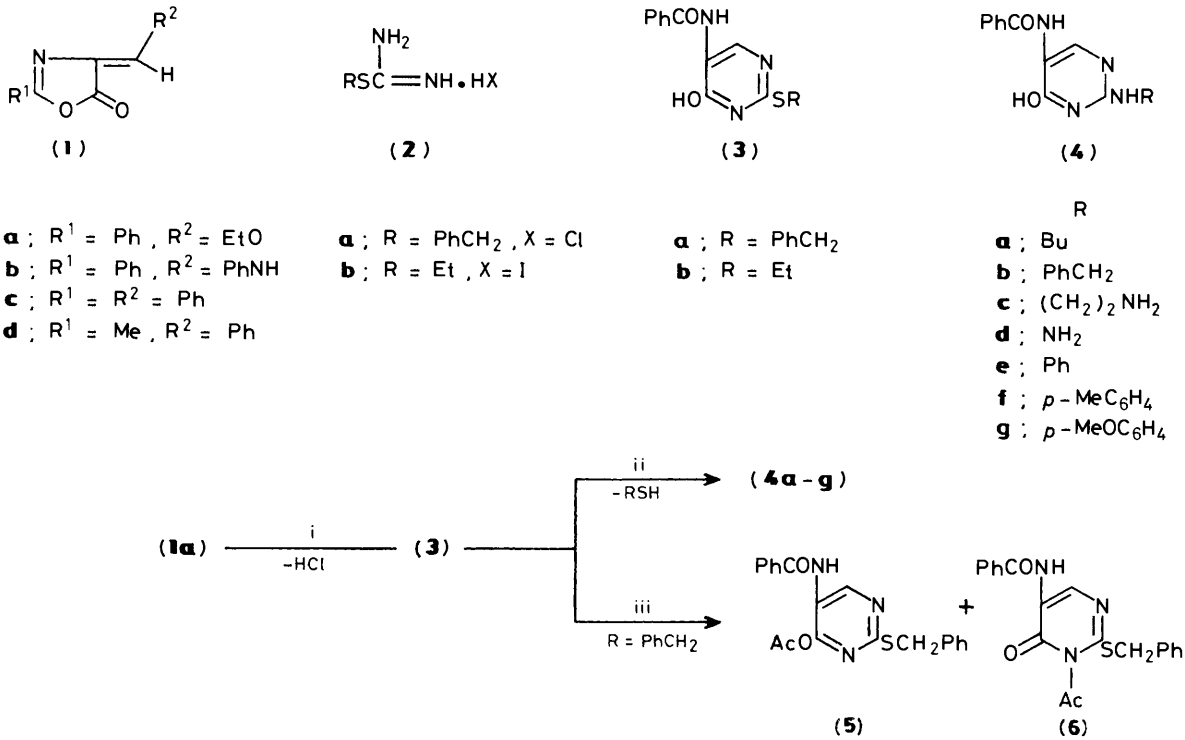
Triethylamine-mediated reactions of *S*-substituted isothiouronium halides (**2**) with unsaturated azlactones (**1**) gave the corresponding *S*-substituted 2-thiopyrimidines (**3**), *S*-substituted 3-thioacrylanilide (**10**), and 4-benzylidene-2-iminoimidazolidin-5-one (**13**), depending on the ethoxy, anilino, and phenyl substituents, respectively, at the 4-C=C bond. Aminolyses of (**3**) afforded 2-aminopyrimidines (**4**). Tautomerism of compounds (**3**) and (**13**) was confirmed by their acetylation and/or hydrolysis. Base-mediated condensation of compound (**1c**) with thiourea or urea in boiling ethanol was unsuccessful, but simple heating of these reactants at an elevated temperature gave 4-benzylidene-2-phenyl-imidazol-5(4*H*)-one (**22**).

Azlactones (**1**) have emerged as an important class of synthons.[1] In order to study the condensation of the azlactone (**1**) with some 1,3-diaminonucleophiles, triethylamine-mediated reactions of *S*-substituted isothiouronium halides (**2**), thiourea, and/or urea with compound (**1**) have now been investigated, using ethanol as a solvent. It has been found that the course of the reaction depends on the nature of the R^2 group in compound (**1**). For example, compound (**1a**) reacted with (**2**) to give *S*-substituted 5-benzoylamino-4-hydroxy-2-thiopyrimidines (**3**), as shown in Scheme 1. Condensations of some (**3a**) into the *N*-acetyl and *O*-acetyl derivatives, (**6**) and (**5**), respectively. Also thiopyrimidines (**3**) have been found to be amenable to aminolyses, thereby providing a convenient method for the synthesis of 2-*N*-substituted 5-acylamino-2-amino-4-hydroxypyrimidines (**4**).

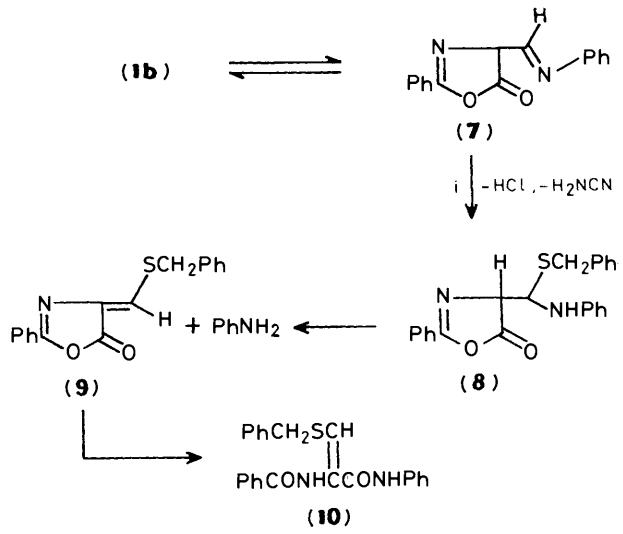
When a mixture of compounds (**1b**) and (**2a**) was heated in ethanol, in the presence of triethylamines, the product was found to be 2-benzoylamino-3-benzylthioacrylanilide (**10**). Evidently, compound (**2a**) decomposed to toluene-α-thiol and cyanamide, and the former attacked the imino tautomer



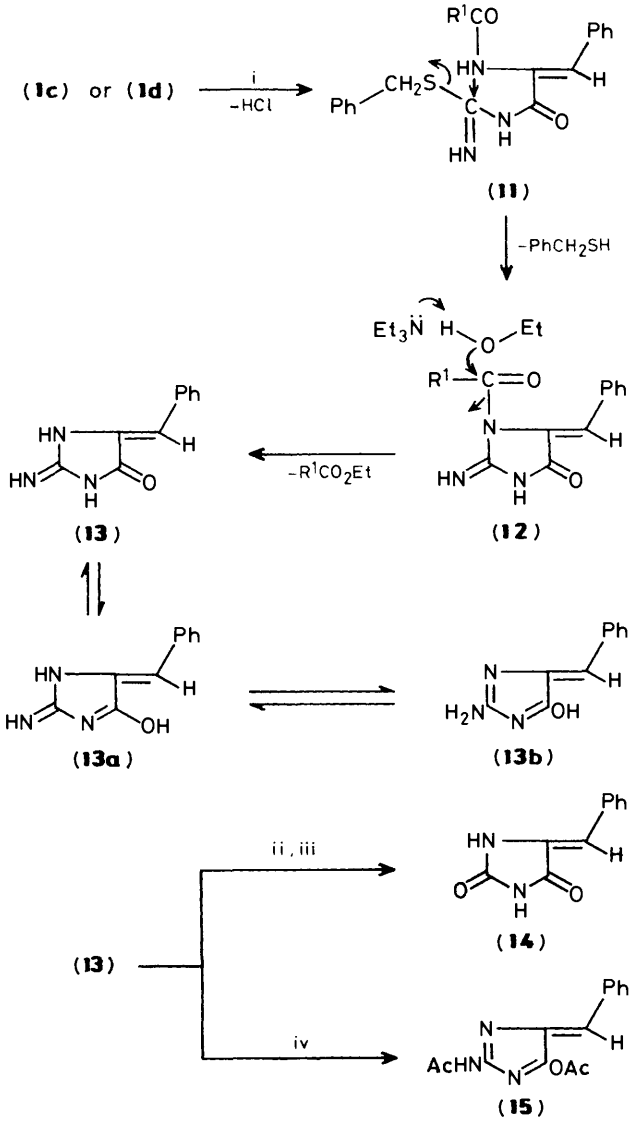
Scheme 1. *Reagents and conditions:* i, (**2**)/Et_3N–EtOH; ii, RNH_2–AcOH, heat; iii, Ac_2O–AcONa

1,3-diamines with (**1a**) are known in the literature,[2,3] but the reaction of *S*-alkylisothiouronium halide with (**1a**) was reported not to give the desired pyrimidine.[2] Possibly, the present milder experimental conditions facilitated the formation of (**3**). These compounds have been found to exist as tautomers, as evident from the facile conversion of compound (**7**) with expulsion of the anilino entity which in turn brought about cleavage of the 1,5-bond of the oxazol-5(4*H*)-one ring (Scheme 2). This pathway was verified by converting (**1b**) into (**10**) with benzyl thiol under similar conditions.

The unsaturated azlactones (**1c**) and (**1d**), under similar con-



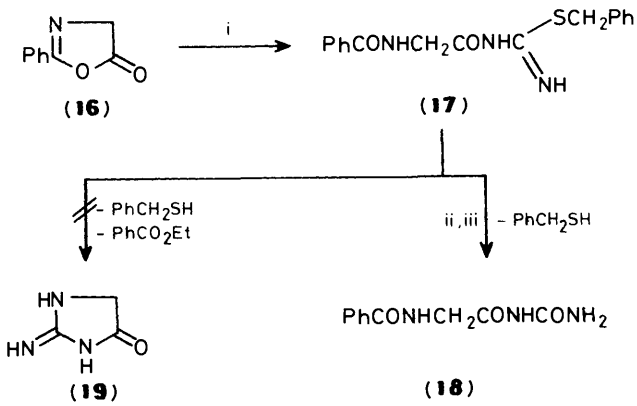
Scheme 2. *Reagents:* i, (**2a**)/Et_3N–EtOH



Scheme 3. *Reagents:* i, (**2a**)/Et_3N–EtOH; ii, NaOH; iii, HCl; iv, Ac_2O–AcONa

ditions, reacted with (**2**) to give a sulphur-free product which has been characterised as the iminoimidazolidinone (**13**) (Scheme 3). This compound exists as tautomers (**13a**) and (**13b**). On hydrolysis by warming with dilute sodium hydroxide solution and/or hydrochloric acid, compound (**13**) gave the (*Z*)-4-benzylidenehydantoin derivative (**14**), whereas acetylation with acetic anhydride and fused sodium acetate afforded a product to which the structure (**15**) was assigned. The stereochemistry of compound (**14**) is based on its u.v. and ^1H n.m.r. spectra (see Table); the $\varepsilon_{max.}$ values in its u.v. spectrum are higher than those of the lower melting isomer (m.p. 219—220 °C) prepared by the known method.[4] At the same time, the signal at δ 6.6 corresponding to the olefinic CH, in its ^1H n.m.r. spectrum, is deshielded in comparison to that of the lower melting isomer for which the value is δ 6.3. It is noteworthy that the aminolysis of unsaturated azlactones, such as (**1c**) or (**1d**), does not affect the stereochemistry at the olefinic centre.[5] In addition, the *Z*-isomer (**1c**) or (**1d**) is more stable than the corresponding *E*-isomer which has been well documented in a recent view.[6] Thus, the conversion of (**1c**) or (**1d**) into (**14**) *via* (**13**) would maintain the steric integrity of the olefinic bond. The compound (**15**) has been previously prepared by the acetic anhydride-mediated cyclocondensation of 2-guanidinocinnamic acid which in its turn was synthesized by the reaction of ethyl phenylglycidate ($PhCHOCO_2Et$) and guanidine.[7] In view of the easy availability of 4-arylmethylene- and 4-alkylidene-oxazol-5(4*H*)-ones, the present method may be useful in the stereospecific synthesis of the corresponding 2-imino-imidazolidin-5-ones and/or hydantoins.

The saturated azlactone (**16**) reacted with compound (**2a**) to give 2-benzylthio-3-hippuroylisothiourea (**17**) which underwent hydrolysis to hippuroylurea (**18**) on warming with aqueous sodium hydroxide (Scheme 4). The attempt to condense (**2**)



Scheme 4. *Reagents:* i, (**2a**)/Et_3N–EtOH; ii, NaOH; iii, HCl

and/or urea with ethyl hippurate was unsuccessful. It appeared that the saturated azlactone (**16**) as well as the unsaturated azlactone (**1c**) underwent 1,5-bond cleavage, but compound (**17**), unlike (**11**), did not cyclise to the creatinine analogue (**19**); the favourable steric disposition of (**11**) towards the cyclisation to (**12**) is the only viable reason. Once the imidazolidinone ring had been formed, the *N*-deacylation followed under the triethylamine-aided generation of ethoxide ions (Scheme 3).

During our investigation of the reaction mechanism, it was found that compound (**1c**) did not react with urea or thiourea in ethanol containing a catalytic amount of potassium hydroxide or triethylamine. Instead, (**1c**) underwent alcoholysis to compound (**21**) which did not react with (**2**), thiourea, and/or urea under similar conditions. However, on simple heating of (**1c**) with urea or thiourea at 160—170 °C for 30 min, 4-benzylidene-

Table. Results of triethylamine-mediated condensation of *S*-substituted isothiouronium halides (**2**), thiourea, and/or urea with azlactones (**1**)/(**16**), and some reactions of the products

Compound[a]	Yield (%)[b]	M.p. (°C)	$\nu_{max.}$(Nujol) (cm^{-1})	Formula	Found (%) (requires) C	H	N
(**3a**)	74	251—253	3 350, 1 660, 1 640	$C_{18}H_{15}N_3O_2S$ (337)	64.25 (64.09)	4.8 (4.45)	12.35 (12.46)
(**3b**)	50	239—240	3 350, 1 670, 1 650	$C_{13}H_{13}N_3O_2S$	56.5 (56.72)	4.35 (4.72)	15.45 (15.27)
(**4a**)	90	269—291	3 350, 1 670, 1 640	$C_{15}H_{18}N_4O_2$	62.65 (62.93)	6.65 (6.29)	19.35 (19.58)
(**4b**)	26 (82)	232—234	3 350, 1 660, 1 640	$C_{18}H_{16}N_4O_2$	67.2 (67.50)	4.9 (5.00)	17.65 (17.50)
(**4c**)	94	243—245	3 350, 3 250, 1 680, 1 640	$C_{13}H_{15}N_5O_2$	57.15 (57.14)	5.25 (5.49)	25.45 (25.64)
(**4d**)	93	245—247	3 350, 3 300, 1 660, 1 640	$C_{11}H_{11}N_5O_2$	54.2 (53.88)	4.75 (4.49)	28.45 (28.57)
(**4e**)	53 (94)	296—298	3 400, 3 300, 1 670, 1 650	$C_{17}H_{14}N_4O_2$	66.5 (66.67)	4.6 (4.58)	18.05 (18.30)
(**4f**)	79 (98)	243—245	3 350, 3 300, 1 660, 1 640	$C_{18}H_{16}N_4O_2$	67.6 (67.50)	5.35 (5.00)	17.75 (17.50)
(**4g**)	80	236—238	3 350, 1 690, 1 660, 1 640	$C_{18}H_{16}N_4O_3$	64.0 (64.28)	4.8 (4.76)	16.4 (16.67)
(**5**)[c]	38	128—130	3 350, 1 740, 1 670, 1 650	$C_{20}H_{17}N_3O_3S$	63.05 (63.32)	4.6 (4.48)	11.25 (11.08)
(**6**)	35	205—207	3 350, 1 680, 1 650	$C_{20}H_{17}N_3O_3S$	63.4 (63.32)	4.7 (4.48)	11.25 (11.08)
(**10**)	80	222—224	3 340, 3 250, 1 670, 1 640	$C_{23}H_{20}N_2O_2S$	71.3 (71.13)	5.4 (5.15)	6.95 (7.21)
(**13**)	72	303—305	3 330, 3 270, 1 710, 1 660, 1 650	$C_{10}H_9N_3O$	64.65 (64.17)	4.65 (4.86)	22.65 (22.45)
(**14**)[d,e]	90	230—231	3 400, 3 300, 1 750, 1 710, 1 660	$C_{10}H_8N_2O_2 \cdot H_2O$	57.85 (58.25)	4.85 (4.85)	14.1 (13.59)
(**15**)[f]	90	214—215[7]	3 260, 1 745, 1 690, 1 660	$C_{14}H_{13}N_3O_3$	61.95 (62.00)	4.54 (4.80)	15.65 (15.50)
(**17**)	20	214—215	3 320, 1 695, 1 660, 1 640	$C_{17}H_{17}N_3O_2S$	62.55 (62.38)	5.5 (5.81)	12.5 (12.83)
(**18**)	70	208—210	3 330, 3 200, 1 660, 1 620	$C_{10}H_{11}N_3O_3$	54.5 (54.30)	4.65 (4.98)	19.2 (19.00)
(**21**)[g]	80	149—150[9]	3 260, 1 730, 1 645, 1 635	$C_{18}H_{17}NO_3$	73.1 (73.25)	5.7 (5.76)	5.05 (4.74)
(**22**)	81	279—280[10]	3 140, 1 705, 1 640	$C_{16}H_{12}N_2O \cdot \frac{1}{2}H_2O$	75.0 (74.70)	5.0 (5.06)	10.65 (10.89)

[a] Because of their inadequate solubility, n.m.r. spectra of all the compounds could not be recorded. [b] In some of the reactions, a considerable amount of the starting material was recovered. Yields in parentheses represent the actual conversion. [c] δ($CDCl_3$–TMS) 2.37 (s, 3 H, OCOMe), 4.40 (s, 2 H, SCH_2Ph), 6.22 (s, 1 H, 6-CH), 7.06—8.09 (m, 10 H, ArH), and 8.87 (s, 1 H, exchangeable, CONH). [d] δ([$^2H_6$]DMSO–TMS) 6.60 (s, 1 H, =CH), 7.15—7.75 (m, 6 H, m, one exchangeable, NH and ArH), and 9.00 (s, 1 H, exchangeable, NH); $\lambda_{max.}$(MeOH) (ε × 10^3) 205 (0.921), 230 (0.978), 235 (0.865), and 320 nm (2.82). [e] The compound prepared by the published method[4] has been found to be the *E*-isomer of (**14**). M.p. 219—220 °C; δ([$^2H_6$]DMSO–TMS) 6.30 (s, 1 H, =CH), 7.10—7.60 (m, 6 H, one exchangeable, NH and ArH), and 10.90 (1 H, exchangeable, NH); $\lambda_{max.}$(MeOH) (ε × 10^3) 205 (0.658), 230 (0.82), 235 (0.735), and 325 nm (1.572). [f] δ($CDCl_2$–TMS) 2.66 (s, 3 H, OCOMe), 2.76 (s, 3 H, NHCO*Me*), 7.09 (s, 1 H, =CH), 7.23—8.20 (m, 5 H, ArH), and 10.43 (s, 1 H, exchangeable, CONH). [g] δ($CDCl_3$–TMS) 1.37 (t, 3 H, *Me*CH_2), 4.29 (q, 2 H, MeCH_2), 7.06 (s, 1 H, =CH), and 7.08—7.84 (m, 11 H, one exchangeable, CONH, and ArH).

2-phenylimidazol-5(4*H*)-one (**22**) was obtained in good yield (Scheme 5).

The compounds reported here have been characterised by spectral data and elemental analyses. The relevant physical data are given in the Table.

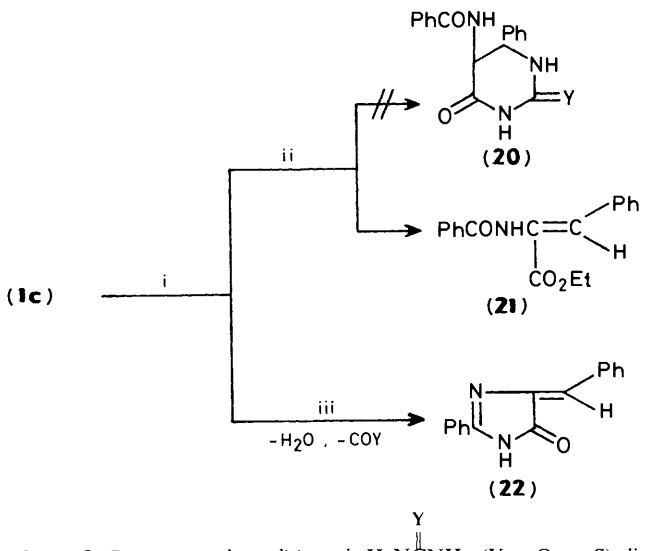
Experimental

M.p.s were determined on a Toshniwal m.p. apparatus and are uncorrected. I.r., ^1H n.m.r., and u.v. spectra were recorded on Perkin-Elmer 720, JEOL FX-90Q and/or Varian FT 80, and Carl-Zeiss Specord spectrophotometers, respectively. Elemental analyses were carried out by Coleman analyser.

Reactions of Unsaturated Azlactones (**1**) *with S-Substituted Isothiouronium Halides* (**2**) *in the Presence of Triethylamine. Formation of Compounds* (**3**), (**10**), *and* (**13**).—A mixture of compound (**1**), (**2**), and triethylamine, in a molar ratio of 1:1:1.5, respectively, was heated under reflux in ethanol [30 ml g^{-1} of (**1**)] for 1—2 h then worked up. Compounds (**3**) and (**10**) were recrystallised from ethanol, and (**13**) was recrystallised from glacial acetic acid. Relevant physical data are given in the Table.

2-Alkyl-/2-Arylamino-5-benzoylamino-4-hydroxypyrimidines (**4**).—A mixture of compound (**3**) and the primary amine, in a molar ratio of 1:1.5, was heated under reflux in glacial acetic acid [50 ml g^{-1} of (**3**)] for 4 h. Work-up and recrystallisation from ethanol gave pure products. See Table for data.

Acetylation of Compounds (**4**) *and* (**13**).—A mixture of compound (**4**) and acetic anhydride [15 ml g^{-1} of (**4**)] was



Scheme 5. *Reagents and conditions:* i, H_2NCNH_2 (Y = O or S); ii, Et_3N–EtOH, heat; iii, 160—170 °C, 30 min

heated under reflux for 3 h, using freshly fused sodium acetate. In the case of (**13**), sodium acetate was not employed and heating was discontinued after 20 min. Work-up and recrystallisation from benzene gave the pure acetyl derivatives. M.p.s, yields, and other data are given in the Table.

Hydrolysis of Compounds (**13**) *and* (**14**).—A mixture of the imidazolidinone (**13**) (500 mg) and aqueous sodium hydroxide (10%, 5 ml) was warmed for 2—3 min over a water bath, cooled, and acidified with conc. HCl to give compound (**14**) which was recrystallised from aqueous ethanol. Physical constants are given in the Table.

Reaction of 2-*Phenyloxazol*-5(4H)-*one* (**16**) *and* (**2a**).—Hippuric acid was cyclised in benzene to compound (**16**) according to the literature procedure,[8] the solvent was completely removed under reduced pressure, and the residue heated with compound (**2a**) and triethylamine in ethanol for 1.5 h. The crude product obtained after work-up was recrystallised from ethanol to give the pure isothiourea (**17**). Relevant data are given in the Table.

Hydrolysis of 2-*Benzyl*-3-*hippuroylisothiourea* (**17**) *to Hippuroylurea* (**18**).—The procedure is the same as that given for the hydrolysis of (**13**). Physical data are given in the Table.

Reactions of Urea/Thioureas with 4-*Benzylidene*-2-*phenyloxazol*-5(4H)-*one* (**1c**). *Formation of Compounds* (**21**) *and* (**22**).—*Method A.* An equimolar mixture of the oxazolone (**1c**), urea/thiourea, and triethylamine was heated under reflux for 2 h in ethanol [20 ml g^{-1} of (**1c**)]. Work-up and recrystallisation from aqueous ethanol gave pure compound (**21**) which was also obtained when the reaction was carried out in the absence of urea or thiourea.

Method B. An equimolar mixture of the oxazolone (**1c**) and urea/thiourea was heated at 160—170 °C for 30 min. The crude product was recrystallised from ethanol to give pure compound (**22**). For the relevant data see the Table.

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