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SYNTHESIS AND TRANSFORMATIONS OF ETHYL (*Z*)-2-(2,3-DIHYDRO-1,3-DIOXO-1H-ISOINDOL-2-YL)-3-(DIMETHYL-AMINO)PROPENOATE*

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Ethyl (Z)-2-(2,3-dihydro-1,3-dioxo-1H-isoindol-2-yl)-3-(dimethylamino)propenoate was prepared in one step from ethyl (2,3-dihydro-1,3-dioxo-1H-isoindol-2-yl)acetate and bis(dimethylamino)-tert-butoxymethane and treated with various amines and hydrazines to afford the corresponding amino substituted products. Reactions of the titled compound with N,N'-, C,N-, and C,O'-ambident nucleophiles in refluxing acetic acid furnished the corresponding fused pyrimidinones, quinolizinones, and pyranones.

Keywords: amines, enaminones, isoindole, pyranones, pyrimidinones, quinolizinones, cyclizations.

Quinolizines [1], pyridopyrimidines [2], 2H-pyran-2-ones [3], and related systems are the constituents of many naturally occurring compounds and their synthetic derivatives exhibiting various biological activities. Such examples of important heterocyclic compounds are aminosubstituted fused heterocyclic systems with a bridgehead nitrogen atom which have been utilized as versatile scaffolds and peptide mimetics [4] (Fig. 1).

Alkyl 2-acylamino-3-(dimethylamino)propenoates are an important subclass of 2-substituted alkyl 3-(dimethylamino)propenoates and their cyclic analogs which are easily available, efficient, and versatile reagents for the preparation of a variety of heterocyclic systems. Alkyl 2-acylamino-3-(dimethylamino)propenoates were employed as reagents in one step syntheses of alkyl 2-acylamino-3-(substituted amino)propenoates as α,β-dehydro-α-amino acid derivatives, and heterocycles with incorporated

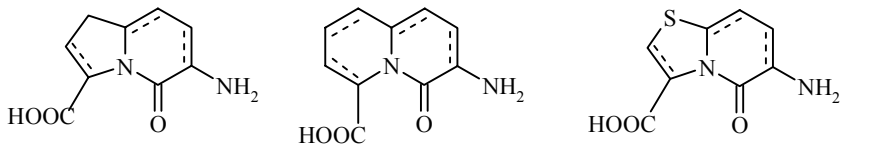

Fig. 1. Some examples of heterocyclic systems as scaffolds for peptide mimetics

* Dedicated to Professor Edmunds Lukevics on the occasion of his 65th birthday.

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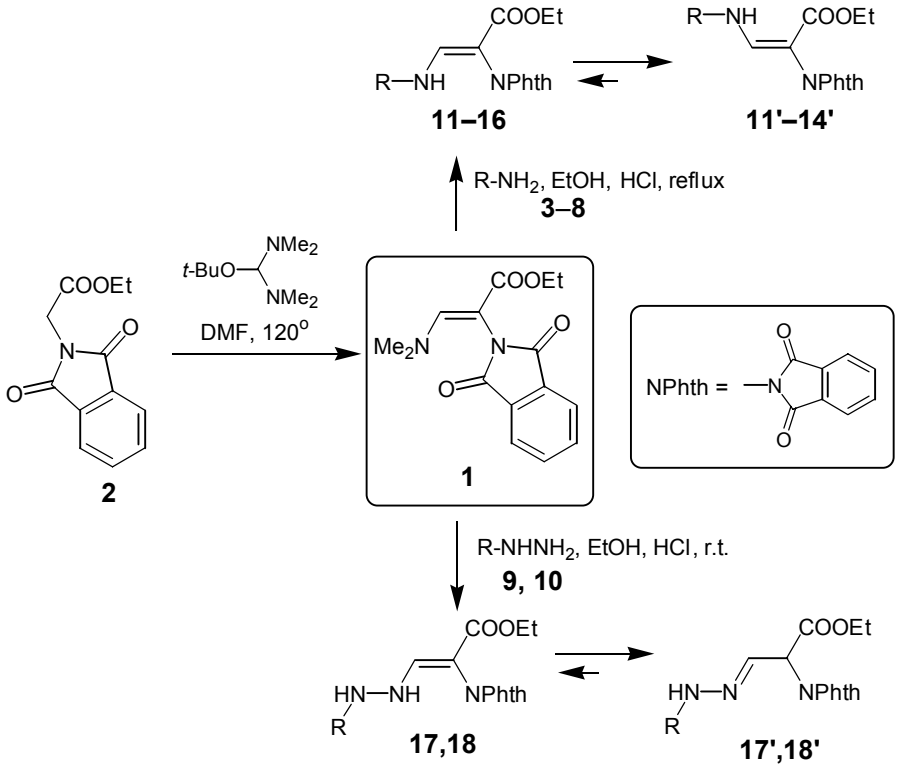
α-amino acid structural element. In this manner, various heterocyclic systems, such as acylamino-substituted azolo- and azino-fused pyridinones, pyrimidinones, pyranones, and their tetrahydro analogs, have been prepared. To date, several reviews on this topic have been published [5, 6]. In continuation of our research, we report the preparation of ethyl (*Z*)-2-(2,3-dihydro-1,3-dioxo-1H-isoindol-2-yl)-3-(dimethylamino)propenoate (**1**) and its transformations with amines, hydrazines, and ambident 1,3-dinucleophiles into phthaloylimino substituted propenoates and heterocyclic systems, which can be deprotected with hydrazine hydrate to give free amino compounds.

Results and Discussion

Ester **1** was prepared in 93% yield from ethyl 2-(2,3-dihydro-1,3-dioxo-1H-isoindol-2-yl)acetate (**2**) and bis(dimethylamino)-*tert*-butoxymethane (Bredereck's reagent). Treatment of **1** with amines **3**-**8** or 3-hydrazinopyridazines **9**, **10** in refluxing ethanol in the presence of equimolar amounts of hydrochloric acid proceeded by substitution of the dimethylamino group.

Scheme 1



Compound	R	Ratio of isomers (in DMSO-d_6)
3, **11**, **11'**	4-Methylphenyl	**11** : **11'** = 83 : 17
4, **12**, **12'**	Thiazol-2-yl	**12** : **12'** = 88 : 12
5, **13**, **13'**	4-Methylpyridin-2-yl	**13** : **13'** = 90 : 10
6, **14**, **14'**	5-Chloropyridin-2-yl	**14** : **14'** = 75 : 25
7, **15**, **15'**	4-Methylpyrimidin-2-yl	**15** : **15'** = 100 : 0
8, **16**, **16'**	6-Chloropyridazin-3-yl	**16** : **16'** = 100 : 0
9, 17, **17'**	6-Chloropyridazin-3-yl	**17** : **17'** = 88 : 12
10, **18**, **18'**	6-Phenylpyridazin-3-yl	**18** : **18'** = 88 : 12

With amines **3**-**8** the corresponding substitution products, ethyl 2-(2,3-dihydro-1,3-dioxo-1H-isoindol-2-yl)-3-(substituted amino)propenoates **11**-**16,** were prepared in 13-80% yields. Propenoates **11**-**14** exist in DMSO-d_6 solution as mixtures of the major (*Z*)-isomers (**11**-**14**) and the minor (*E*)-isomers (**11'**-**14'**), while propenoates **2**, **15**, and **16** exist in DMSO-d_6 solution as the (*Z*)-isomers, exclusively. Similarly, acid catalyzed treatment of **1** with 3-hydrazinopyridazine derivatives **9**, **10** in ethanol at room temperature afforded 3-hydrazinopropenoates **17**, **18**. In DMSO-d_6 solution, equilibrium between the hydrazines **17**, **18** as the major and their hydrazono forms as the minor tautomers **17'**, **18'**, respectively, was established (Scheme 1).

On the other hand, heating of ethyl (*Z*)-2-(2,3-dihydro-1,3-dioxo-1H-isoindol-2-yl)-3-(dimethylamino)propenoate (**1**) in acetic acid with 2-aminothiazole (**4**), 2-amino-4-methylpyridine (**5**), and 2-aminopyridine (**19**) as N,N'-ambident nucleophiles afforded the corresponding pyrimidinones **20**-**22** in 15-64% yield. Similarly, treatment with ethyl 2-pyridineacetate (**23**) and 2-pyridineacetonitrile (**24**) as C,N-ambident nucleophiles furnished quinolizinone derivatives **25**, **26**, while with C,O-ambident nucleophiles, such as ethyl acetoacetate (**27**), 1,3-cyclohexanedione (**28**), 5,5-dimethyl-1,3-cyclohexanedione (**29**), 4-hydroxy-2-pyridone (**30**), and 4-hydroxy-6-methyl-2H-pyran-2-one (**31**), the corresponding fused pyranones **32**-**36** were obtained in 46-81% yield (Scheme 2).

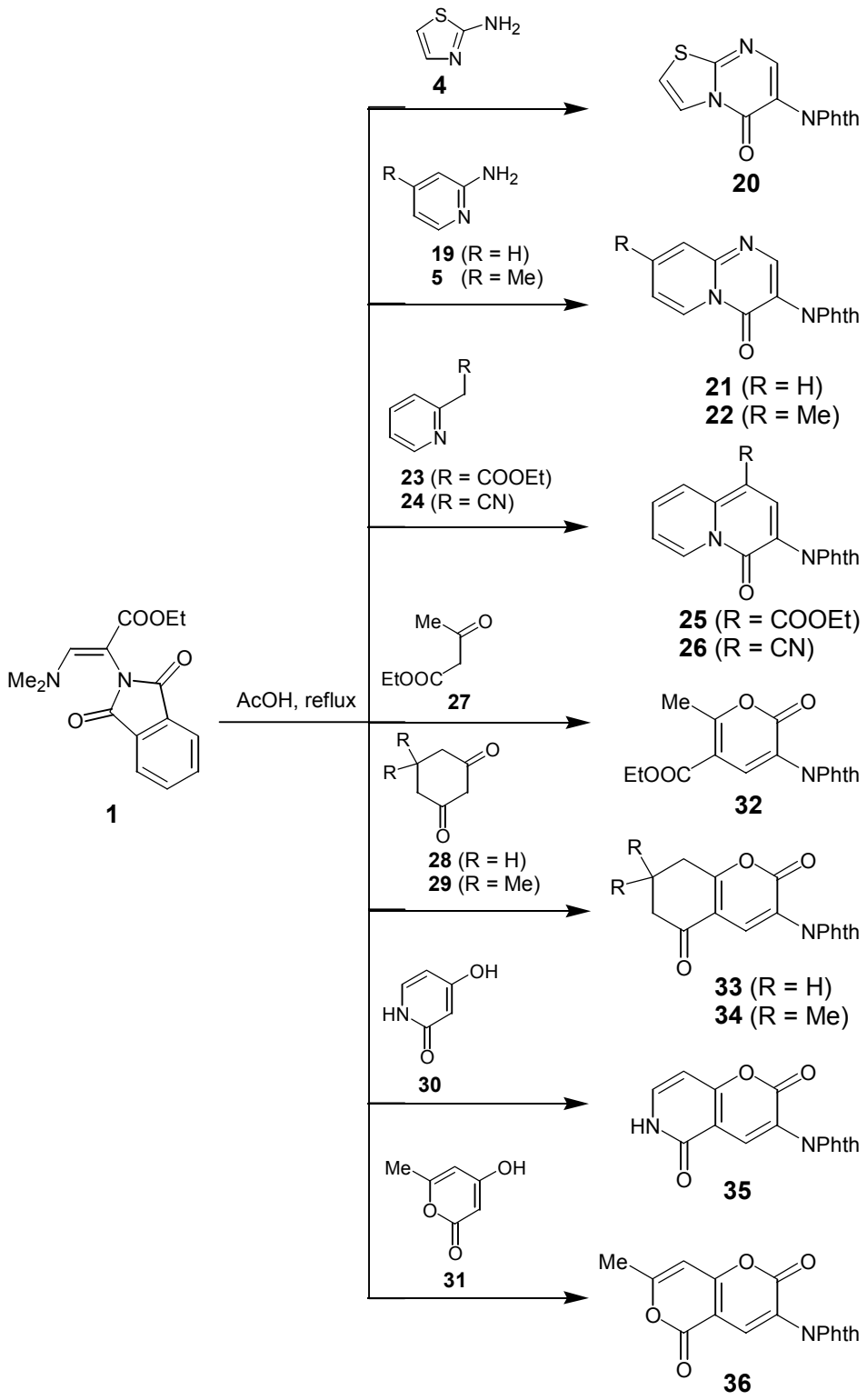
Heating of **1** with 1,3-cyclopentanedione (**37**) or with 1,3-dimethylbarbituric acid (**38**) in acetic acid under reflux resulted in decomposition of starting material giving inseparable mixtures as products. However, upon heating at 80-100° the corresponding propenoates **39**, **40** were obtained in the form of dimethylammonium salts. Formation of salts **39**, **40** offers additional evidence of the mechanism of dimethylamine substitution, which, according to our previous observations, proceeds *via* addition-elimination mechanism. In some cases, the adducts have also been isolated [7]. The difference between the propenoates **39**, **40** and the adducts **41**, **42** as intermediates with the same molecular formula was clearly seen in the ^{1}H NMR spectra, where the protons at the 3-position, i.e., the proton attached to the double bond, in compounds **39** and **40** appeared as singlets with chemical shifts δ 7.71 and 8.25 ppm, respectively (Scheme 3).

3-(2,3-Dihydro-1,3-dioxo-1H-isoindol-2-yl)-4H-pyrido[1,2-*a*]pyrimidin-4-one (**21**) and ethyl 3-(2,3-dihydro-1,3-dioxo-1H-isoindol-2-yl)-4H-quinolizin-4-one-1-carboxylate (**25**) were treated with hydrazine hydrate in refluxing ethanol in order to achieve the deprotection of the amino group at the 3-position. In both cases, the corresponding free amino compounds, 3-amino-4H-pyrido[1,2-*a*]- pyrimidin-4-one (**43**) and 3-amino-4H-quinolizin-4-one (**44**), were obtained in 86 and 28% yield, respectively (Scheme 4).

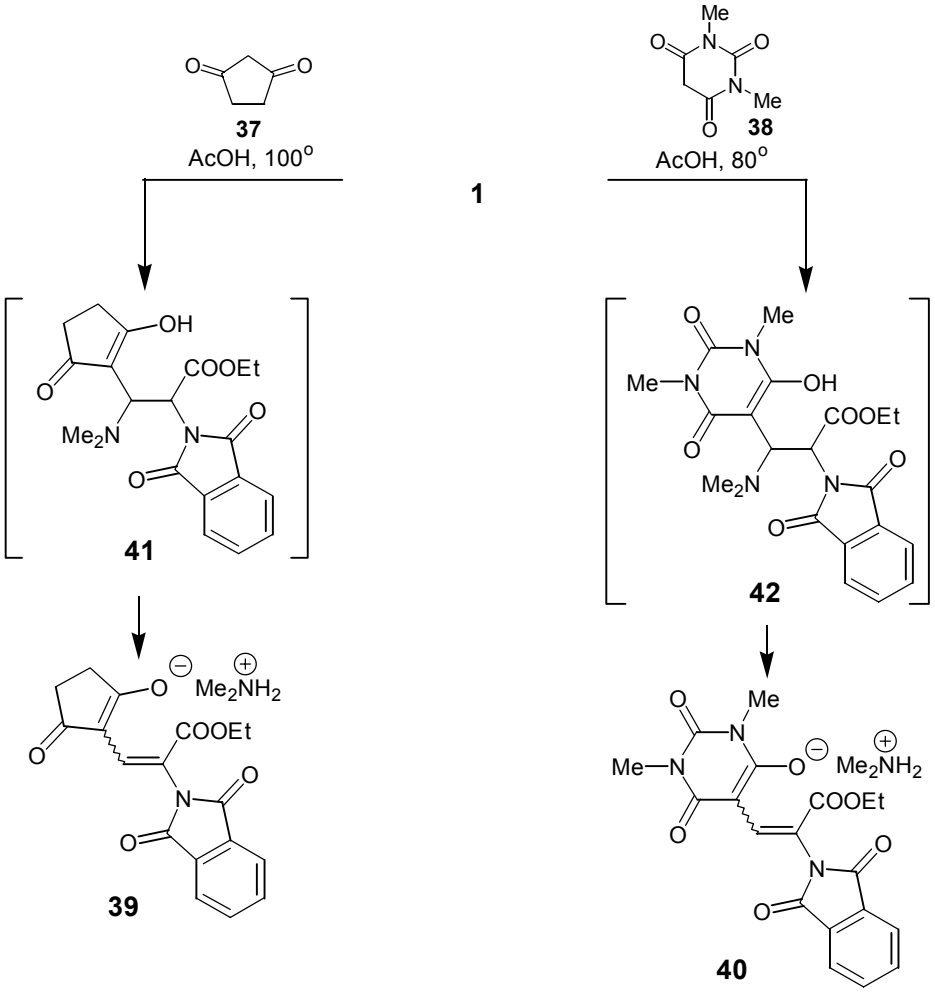
The structures of novel compounds **1**, **11**-**18**, **20**-**22**, **25**, **26**, **32**-**36** were confirmed by spectroscopic methods and by elemental analyses for C, H, and N. Their spectral data are in agreement with the literature data for closely related compounds [5, 6].

The configuration around the C=C double bond in compound **1** was determined by NMR (HMBC technique) on the basis of the magnitude of the long-range heteronuclear coupling constant, $^3J_{C–H}$ = 3.0 Hz, which indicated the *cis*-relationship between the proton at the position 3 and the carbonyl carbon atom at the position 1. For compound **13**, which exists in DMSO-d_6 solution as a mixture of the (*Z*)-isomer **13** and (*E*)-isomer **13'** in a ratio of 90:10, respectively, the isomerization around the C=C double bond in DMSO-d_6 solution was also confirmed by HMBC experiment which showed different magnitudes of heteronuclear coupling constants: $^3J_{C–H}$ = 2.5 Hz for the (*Z*)-isomer **13** and $^3J_{C–H}$ = 9.0 Hz for the (*E*)-isomer **13'**. $^3J_{C–H}$ Coupling constants are in agreement with previously observed ^3J values for the (*Z*)- and (*E*)-isomers of closely related propenoates [8-10] (Fig. 2). The structure of compound **1** was also confirmed by X-ray diffraction (Fig. 3).

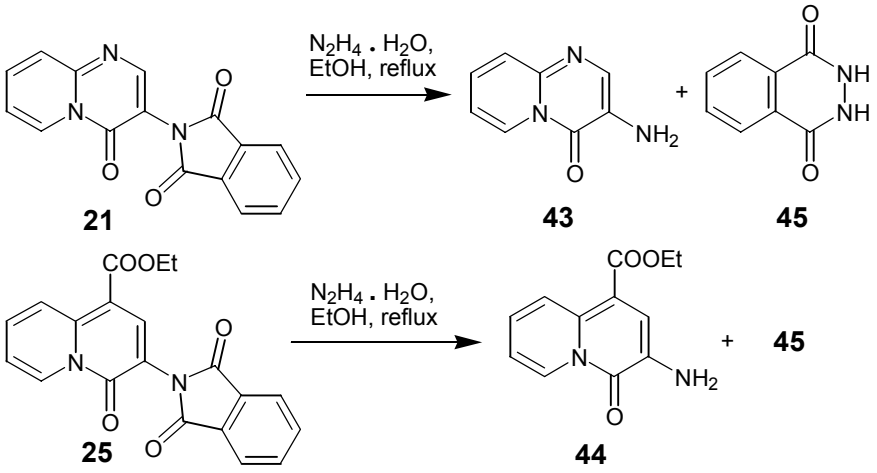
Scheme 2


4
20
19 (R = H)
5 (R = Me)
21 (R = H)
22 (R = Me)
23 (R = COOEt)
24 (R = CN)
25 (R = COOEt)
26 (R = CN)
27
AcOH, reflux
1
32
28 (R = H)
29 (R = Me)
33 (R = H)
34 (R = Me)
30
35
31
36

Scheme 3



Scheme 4



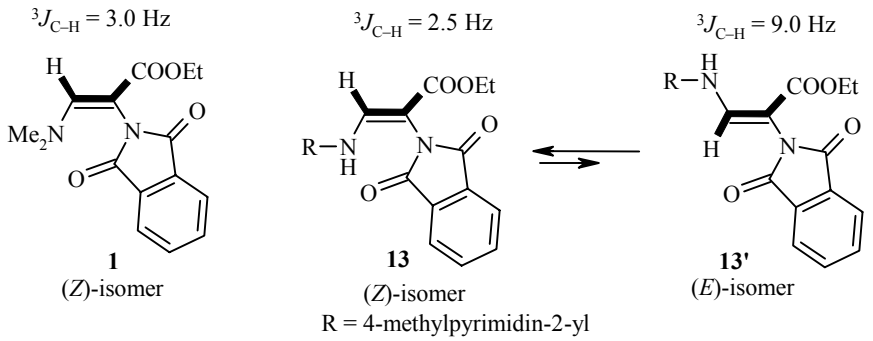


Fig. 2. NMR determination of configuration around the C=C double bond in compounds **1** and **13** by the 2D HMBC technique.

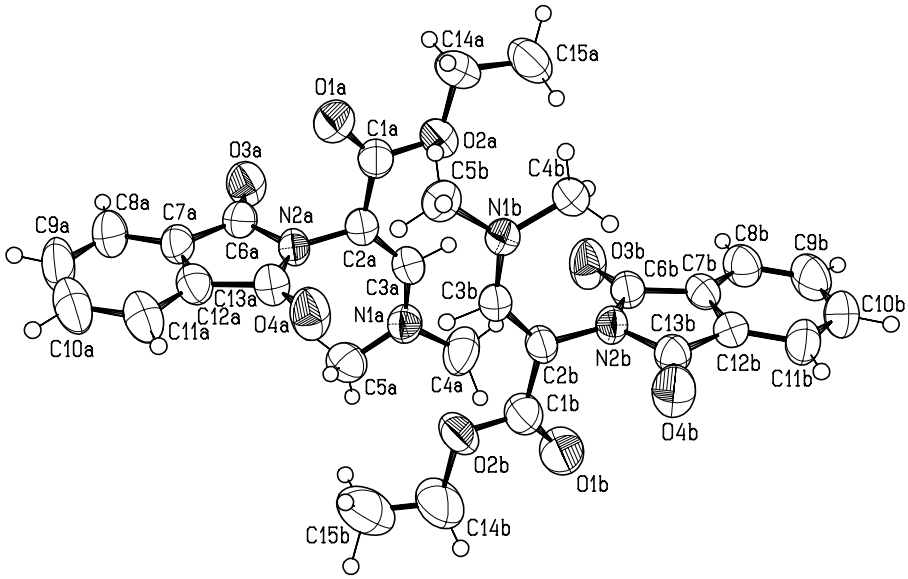


Fig. 3. Ortep view of the asymmetric unit of **1** with labelling of non-hydrogen atoms. (Ellipsoids are drawn at 50% probability level.)

TABLE 1. Crystallographic data for compound **1**

Crystal data	
1	2
Chemical formula	$C_{15}H_{16}N_2O_4$
Relative weight	288.3
Crystal system	monoclinic
Space group	$P2_1/c$, No. 14
a, Å	11.630(1)
b, Å	8.343(1)
c, Å	13.069(1)
β (°)	96.49(1)
V, Å^3	2978.7(8)
Z	4

TABLE 1 (continued)

1	2
Calc. density D_x, $Mg \cdot m^{-3}$	1.286
Radiation type	MoKα
Wavelength, Å	0.71069
No. of refl. for cell param.	75
θ range (°) for cell param.	10.0-17.9
μ, mm^{-1}	0.094
Temperature, K	293(1)
Crystal shape	prism
Crystal size, mm	0.40×0.32×0.32
Crystal color	yellow
Data collection	
Diffractometer	Enraf Nonius CAD-4
Data collection method	ω-2θ scans
Absorption correction	None
No. of measured refl.	18826
No. of independent refl.	5850
No. of observed refl.	3108
Criterion of observed refl.	$I > 2.5\sigma(I)$
R_{int}	0.023
θ_{max} (°)	26
Range of *h*, *k*, *l*	$-13 \rightarrow h \rightarrow 13$ $-13 \rightarrow k \rightarrow 19$ $-20 \rightarrow l \rightarrow 20$
Intensity decay (%)	0.37
Refinement	
Refinement on	*F*
R	0.068
wR	0.073
No. of contributing refl.	4614
No. of parameters	484
$(\Delta/\sigma)_{max}$	0.0097
$\Delta\rho_{max}$, eA^{-3}	0.494
$\Delta\rho_{min}$, eA^{-3}	-0.457

TABLE 2. Bond distances with e.s.d.'s in parentheses for compound **1**

Bond	*d*, Å	Bond	*d*, Å
1	2	3	4
C(1a)–C(2a)	1.456(6)	C(1b)–C(2b)	1.442(6)
C(2a)–C(3a)	1.361(5)	C(2b)–C(3b)	1.349(5)
C(6a)–C(7a)	1.474(6)	C(6b)–C(7b)	1.485(5)
C(7a)–C(8a)	1.388(6)	C(7b)–C(8b)	1.377(6)
C(7a)–C(12a)	1.378(6)	C(7b)–C(12b)	1.376(5)
C(8a)–C(9a)	1.389(9)	C(8b)–C(9b)	1.379(7)
C(9a)–C(10a)	1.37(1)	C(9b)–C(10b)	1.375(8)
C(10a)–C(11a)	1.384(8)	C(10b)–C(11b)	1.371(7)
C(11a)–C(12a)	1.377(7)	C(11b)–C(12b)	1.377(6)
C(12a)–C(13a)	1.482(5)	C(12b)–C(13b)	1.481(5)

TABLE 2 (continued)

1	2	3	4
C(14a)–C(15a)	1.480(8)	C(14b)–C(15b)	1.43(1)
O(1a)–C(1a)	1.210(5)	O(1b)–C(1b)	1.213(5)
O(2a)–C(1a)	1.352(5)	O(2b)–C(1b)	1.333(6)
O(2a)–C(14a)	1.451(6)	O(2b)–C(14b)	1.451(9)
O(3a)–C(6a)	1.202(5)	O(3b)–C(6b)	1.209(5)
O(4a)–C(13a)	1.210(5)	O(4b)–C(13b)	1.193(5)
N(1a)–C(3a)	1.326(5)	N(1b)–C(3b)	1.329(5)
N(1a)–C(4a)	1.449(7)	N(1b)–C(4b)	1.459(6)
N(1a)–C(5a)	1.448(6)	N(1b)–C(5b)	1.452(6)
N(2a)–C(2a)	1.424(4)	N(2b)–C(2b)	1.436(4)
N(2a)–C(6a)	1.398(5)	N(2b)–C(6b)	1.379(5)
N(2a)–C(13a)	1.391(5)	N(2b)–C(13b)	1.407(5)

TABLE 3. Bond angles with e.s.d.'s in parentheses for compound **1**

Angle	ω,deg.	Angle	ω,deg.
C(1a)–O(2a)–C(14a)	116.3(3)	C(1b)–O(2b)–C(14b)	115.7(4)
C(3a)–N(1a)–C(4a)	119.6(4)	C(3b)–N(1b)–C(4b)	123.4(3)
C(3a)–N(1a)–C(5a)	124.5(4)	C(3b)–N(1b)–C(5b)	120.5(3)
C(4a)–N(1a)–C(5a)	115.9(4)	C(4b)–N(1b)–C(5b)	116.0(4)
C(2a)–N(2a)–C(6a)	123.9(3)	C(2b)–N(2b)–C(6b)	125.0(3)
C(2a)–N(2a)–C(13a)	123.3(3)	C(2b)–N(2b)–C(13b)	122.5(3)
C(6a)–N(2a)–C(13a)	110.9(3)	C(6b)–N(2b)–C(13b)	111.4(3)
O(1a)–C(1a)–O(2a)	122.4(4)	O(1b)–C(1b)–O(2b)	121.8(4)
O(1a)–C(1a)–C(2a)	124.1(4)	O(1b)–C(1b)–C(2b)	124.5(4)
O(2a)–C(1a)–C(2a)	113.5(3)	O(2b)–C(1b)–C(2b)	113.6(4)
N(2a)–C(2a)–C(1a)	112.5(3)	N(2b)–C(2b)–C(1b)	113.2(3)
N(2a)–C(2a)–C(3a)	124.6(3)	N(2b)–C(2b)–C(3b)	124.7(3)
C(1a)–C(2a)–C(3a)	122.9(3)	C(1b)–C(2b)–C(3b)	122.0(3)
N(1a)–C(3a)–C(2a)	131.8(4)	N(1b)–C(3b)–C(2b)	131.6(3)
O(3a)–C(6a)–N(2a)	124.0(4)	O(3b)–C(6b)–N(2b)	125.1(3)
O(3a)–C(6a)–C(7a)	129.9(4)	O(3b)–C(6b)–C(7b)	128.3(3)
N(2a)–C(6a)–C(7a)	106.1(3)	N(2b)–C(6b)–C(7b)	106.6(3)
C(6a)–C(7a)–C(8a)	130.8(4)	C(6b)–C(7b)–C(8b)	130.7(4)
C(6a)–C(7a)–C(12a)	108.7(3)	C(6b)–C(7b)–C(12b)	107.8(3)
C(8a)–C(7a)–C(12a)	120.5(4)	C(8b)–C(7b)–C(12b)	121.5(4)
C(7a)–C(8a)–C(9a)	116.6(5)	C(7b)–C(8b)–C(9b)	117.4(4)
C(8a)–C(9a)–C(10a)	122.6(6)	C(8b)–C(9b)–C(10b)	121.0(5)
C(9a)–C(10a)–C(11a)	120.6(6)	C(9b)–C(10b)–C(11b)	121.4(5)
C(10a)–C(11a)–C(12a)	117.3(5)	C(10b)–C(11b)–C(12b)	117.9(5)
C(7a)–C(12a)–C(11a)	122.4(4)	C(7b)–C(12b)–C(11b)	120.8(4)
C(7a)–C(12a)–C(13a)	107.5(3)	C(7b)–C(12b)–C(13b)	108.6(3)
C(11a)–C(12a)–C(13a)	130.1(4)	C(11b)–C(12b)–C(13b)	130.6(4)
O(4a)–C(13a)–N(2a)	125.0(4)	O(4b)–C(13b)–N(2b)	124.4(3)
O(4a)–C(13a)–C(12a)	128.4(4)	O(4b)–C(13b)–C(12b)	130.0(4)
N(2a)–C(13a)–C(12a)	106.6(3)	N(2b)–C(13b)–C(12b)	105.6(3)
O(2a)–C(14a)–C(15a)	107.7(5)	O(2b)–C(14b)–C(15b)	110.0(6)

EXPERIMENTAL

All starting materials and solvents were commercially available (in most cases from Fluka AG) and purified following the standard techniques. Melting points were taken with a Kofler micro hot stage. The ^{1}H and ^{13}C NMR spectra were obtained with a Bruker Avance DPX 300 (300 MHz) spectrometer with DMSO-d_6 and $CDCl_3$ as solvents and Me_4Si as internal standard. IR spectra were recorded with a Perkin-Elmer Spectrum BX FTIR instrument (KBr discs). The microanalyses for C, H, and N were obtained with a Perkin-Elmer CHN Analyser 2400. TLC: Merck, Alufolien Kieselgel 60 F 254, 0.2 mm. Ethyl (2,3-dihydro-1,3-dioxo-1H-isoindol-2-yl)acetate (**2**) was prepared according to the procedure described in the literature [11].

Ethyl (*Z*)-2-(2,3-Dihydro-1,3-dioxo-1H-isoindol-2-yl)-3-(dimethylamino)propenoate (1). A mixture of ethyl (2,3-dihydro-1,3-dioxo-1H-isoindol-2-yl)acetate (**2**) (2.332 g, 10 mmol), bis(dimethylamino)-*tert*-butoxymethane (3 ml, 15 mmol), and dimethylformamide (4 ml) was stirred under argon at 120°C for 4 h. Volatile components were evaporated in vacuo and the oily residue was cooled to -15°C. Diethyl ether (5 ml) and water (~5 drops) were added and the precipitate was collected by filtration and crystallized from methanol–water to give **1**. Yield 93% (2.685 g), yellow crystals; mp 124-126°C (methanol–water). IR, ν, cm^{-1}: 1780, 1680 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz), δ, ppm, *J* (Hz): 1.08 (3H, t, *J* = 7.0, $OCH_2C\underline{H}_3$); 2.89 (6H, s, NMe_2); 4.00 (2H, q, *J* = 7.0, $OC\underline{H}_2CH_3$); 7.69 (1H, s, 3-H); 7.89- 7.97 (4H, m, phthaloyl). ^{13}C NMR (DMSO-d_6, 75.5 MHz), δ, ppm, *J* (Hz): 15.3; 41.2; 60.1; 88.66; 124.5; 132.4; 135.8; 149.9; 166.0; 169.5. Found, %: C 62.78; H 5.39; N 9.44. $C_{15}H_{16}N_2O_4$. Calculated, %: C 62.49; H 5.59; N 9.72.

General Procedure for the Preparation of Ethyl 2-(2,3-Dihydro-1,3-dioxo-1H-isoindol-2-yl)-3-(N-substituted amino)propenoates (11-16). Hydrochloric acid (37%, 3 drops, ~1 mmol) was added to a solution of **1** (288 mg, 1 mmol) and amine **3-8** (1 mmol) in anhydrous ethanol (3 ml) and the reaction mixture was stirred at 20-80°C for 1-12 h. The precipitate was collected by filtration, washed with a small amount of anhydrous ethanol, and crystallized from an appropriate solvent. The following compounds were prepared in this manner:

Ethyl 2-(2,3-Dihydro-1,3-dioxo-1H-isoindol-2-yl)-3-[(4-methylphenyl)amino]propenoate (11) was prepared from **1** and 4-methylaniline (**3**); reflux for 1 h. Yield 80% (279 mg); mp 256-262°C (ethanol–water). IR, ν, cm^{-1}: 3310 (NH), 1710, 1670 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz), δ, ppm, *J* (Hz): major isomer **11**: 1.17 (3H, t, *J* = 7.0, $OCH_2C\underline{H}_3$); 2.26 (s, 3H, Me–Ar); 4.09 (2H, q, *J* = 7.0, $OC\underline{H}_2CH_3$); 7.05 (2H, d, *J* = 8.3, 2H of Ar); 7.14 (2H, d, $J_{H2–H3}$ = 8.3, 2H of Ar); 7.89-7.98 (4H, m, phthaloyl); 8.19 (1H, d, *J* = 13.6, 3-H); 9.45 (1H, d, *J* = 13.6, NH); minor isomer **11'**: 1.11 (3H, t, *J* = 7.0, $OCH_2C\underline{H}_3$); 2.25 (3H, s, Me–Ar); 4,12 (2H, q, *J* = 7.0, $OC\underline{H}_2CH_3$); 8.02 (1H, d, *J* = 12.4, 3-H); 9.82 (1H, d, *J* = 12.4, NH). Found, %: C 68.87; H 5.04; N 7.92. $C_{20}H_{18}N_2O_4$. Calculated, %: C 68.56; H 5.18; N 8.00.

Ethyl 2-(2,3-Dihydro-1,3-dioxo-1H-isoindol-2-yl)-3-[(thiazol-2-yl)amino]propenoate (12) was prepared from **1** and 2-aminothiazole (**4**); refluxed for 12 h. Yield 22% (75 mg); mp 223-225°C (ethanol). IR, ν, cm^{-1}: 3260 (NH), 1710, 1670 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz), δ, ppm, *J* (Hz): major isomer **12**: 1.19 (3H, t, *J* = 7.0, $OCH_2C\underline{H}_3$); 4.14 (2H, q, *J* = 7.0, $OC\underline{H}_2CH_3$); 7.16 (1H, d, *J* = 3.4, 4'-H); 7.38 (1H, d, *J* = 3.4, 5'-H); 7.92-8.02 (4H, m, phthaloyl); 8.50 (1H, d, *J* = 9.4, 3-H); 11.00 (d, 1H, $J_{CH–NH}$ = 11.7, NH); minor isomer **12'**: 7.20 (1H, d, *J* = 3.4, 4'-H); 7.36 (d, 1H, *J* = 3.4, 5'-H). Found, %: C 55.62; H 3.97; N 11.94. $C_{16}H_{13}N_3O_4S$. Calculated, %: C 55.97; H 3.82; N 12.24.

Ethyl 2-(2,3-Dihydro-1,3-dioxo-1H-isoindol-2-yl)-3-[(4-methylpyridin-2-yl)amino]propenoate (13) was prepared from **1** and 2-amino-4-methylpyridine (**5**); refluxed for 5 h. Yield 13% (45 mg), mp 254-258°C (ethanol). IR, ν, cm^{-1}: 3300 (NH), 1710, 1660 (C=O), 1300. ^{1}H NMR (DMSO-d_6, 300 MHz), δ, ppm, *J* (Hz): major isomer **13**: 1.19 (3H, t, *J* = 7.0, $OCH_2C\underline{H}_3$); 2.24 (3H, s, 4'-Me); 4.13 (2H, q, *J* = 7.0, $OC\underline{H}_2CH_3$); 6.69 (1H, d, *J* = 1.5, 3'-H); 6.87 (1H, dd, *J* = 1.4; 5.2, 5'-H); 7.92-8.00 (4H, m, phthaloyl); 8.17 (1H, d, *J* = 5.2, 6'-H); 8.86 (1H, d, *J* = 12.8, 3-H); 9.94 (1H, d, *J* = 12.8, NH); minor isomer **13'**: 1.06 (3H, t, *J* = 7.0, $OCH_2C\underline{H}_3$); 2.09 (3H, s, 4'-Me); 4.33 (2H, q, *J* = 7.0, $OC\underline{H}_2CH_3$). Found, %: C 64.62; H 4.75; N 11.64. $C_{19}H_{17}N_3O_4$. Calculated, %: C 64.95; H 4.88; N 11.96.

Ethyl 2-(2,3-Dihydro-1,3-dioxo-1H-isoindol-2-yl)-3-[(5-chloropyridin-2-yl)amino]propenoate (14) was prepared from **1** and 2-amino-5-chloropyridine (**6**); refluxed for 10 h. Yield 45% (168 mg); mp 263-268°C (methanol). IR, ν, cm^{-1}: 3290 (NH), 1710, 1660 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz), δ, ppm, *J* (Hz): major isomer **14**: 1.18 (3H, t, *J* = 7.0, $OCH_2C\underline{H}_3$); 4.17 (2H, q, *J* = 7.0, $OC\underline{H}_2CH_3$); 6.90 (1H, d, *J* = 8.8, 3'-H); 7.81 (1H, dd, *J* = 2.6; 8.8, 4'-H); 7.93-8.01 (4H, m, phthaloyl); 8.36 (1H, d, *J* = 2.6, 6'-H); 8.78 (1H, d, *J* = 12.1, 3-H); 10.18 (1H, d, *J* = 12.1, NH); minor isomer **14'**: 1.12 (3H, t, *J* = 7.0, $OCH_2C\underline{H}_3$); 4.17 (2H, q, *J* = 7.0, $OC\underline{H}_2CH_3$); 7.44 (1H, d, *J* = 8.8, 3'-H); 8.29 (1H, d, *J* = 12.5, 3-H); 10.30 (1H, d, *J* = 12.4, NH). Found, %: C 57.85, H 3.65, N 10.99. $C_{18}H_{14}ClN_3O_4$. Calcd., %: C 58.15, H 3.80, N 11.30.

Ethyl 2-(2,3-Dihydro-1,3-dioxo-1H-isoindol-2-yl)-3-[(4-methylpyrimidin-2-yl)amino]propenoate (15) was prepared from **2** and 2-amino-4-methylpyrimidine (**7**); refluxed for 2 h. Yield 31% (109 mg); mp 233-246°C (ethanol). IR, ν, cm^{-1}: 3280 (NH), 1710, 1670 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz), δ, ppm, *J* (Hz): 1.19 (3H, t, *J* = 7.0, $OCH_2C\underline{H}_3$); 4.14 (2H, q, *J* = 7.0, $OC\underline{H}_2CH_3$); 7.00 (1H, d, *J* = 5.1, 5'-H); 7.88-7.96 (4H, m, phthaloyl); 8.46 (1H, d, *J* = 5.1, 6'-H); 8.80 (1H, d, *J* = 12.4, 3-H); 10.81 (1H, d, *J* = 12.4, NH). Found, %: C 61.50; H 4.54; N 15.70. $C_{18}H_{16}N_4O_4$. Calculated, %: C 61.36; H 4.58; N 15.90.

Ethyl 2-(2,3-Dihydro-1,3-dioxo-1H-isoindol-2-yl)-3-[(6-chloropyridazine-3-yl)amino]propenoate (16) was prepared from **1** and 3-amino-6-chloropyridazine (**8**); refluxed for 7 h. Yield 13% (50 mg); mp 328-330°C (ethanol). IR, ν, cm^{-1}: 3300 (NH), 1710, 1670 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz), δ, ppm, *J* (Hz): 1.21 (3H, t, *J* = 7.0, $OCH_2C\underline{H}_3$); 4,17 (2H, q, *J* = 7.0, $OC\underline{H}_2CH_3$); 7.29 (1H, d, *J* = 9.2, 4'-H); 7.76 (1H, d, *J* = 9.2, 5'-H); 7.94-8.02 (4H, m, phthaloyl); 8.84 (1H, d, *J* = 12.0, 3-H); 10.32 (1H, d, *J* = 11.6, NH). Found, %: C 54.61; H 3.35; N 14.52. $C_{17}H_{13}ClN_4O_4$. Calculated, %: C 54.78; H 3.52; N 15.03.

Ethyl 3-[(6-Chloropyridazin-3-yl)hydrazino]-2-(2,3-dihydro-1,3-dioxo-1H-isoindol-2-yl)propenoate (17). A mixture of compound **1** (288 mg, 1 mmol), 6-chloro-3-hydrazinopyridazine (**9**) (129 mg, 1 mmol), anhydrous ethanol (20 ml), and hydrochloric acid (37%, 3 drops, ~1 mmol) was stirred at room temperature for 3 h. Then water (5 ml) was added and the precipitate was collected by filtration, washed with anhydrous ethanol, and crystallized from ethanol–water to give **17**. Yield 21% (82 mg); mp 186-187°C (ethanol–water). IR, ν, cm^{-1}: 3480 (NH), 1740, 1720 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz), δ, ppm, *J* (Hz): major isomer **17**: 1.14 (3H, t, *J* = 7.0, $OCH_2C\underline{H}_3$); 4.05 (2H, q, *J* = 7.0, $OC\underline{H}_2CH_3$); 7.00 (1H, d, *J* = 9.8, 4'-H); 7.72 (1H, d, *J* = 10.2, 3-H); 7.84-7.96 (4H, m, phthaloyl); 7.92 (1H, d, *J* = 9.8, 5'-H); 9.46 (1H, d, *J* = 10.2, Het–NH–N<u>H</u>); 9.63 (1H, s, Het–N<u>H</u>–NH); minor isomer **17'**: 1.18 (3H, t, *J* = 7.0, $OCH_2C\underline{H}_3$); 4.21 (2H, q, *J* = 7.0, $OC\underline{H}_2CH_3$); 5.77 (1H, d, *J* = 4.9, 2-H); 7.11 (1H, d, *J* = 9.8, 4'-H); 7.55 (1H, d, $J_{H4–H5}$ = 9.8, 5'-H); 7.82 (1H, d, *J* = 4.5, 3-H); 11.65 (1H, s, Het–N<u>H</u>). Found, %: C 52.41; H 3.50; N 17.85. $C_{17}H_{14}ClN_5O_4$. Calculated, %: C 52.65; H 3.64; N 18.06.

Ethyl 2-(2,3-Dihydro-1,3-dioxo-1H-isoindol-2-yl)-3-[(6-phenylpyridazin-2-yl)hydrazino]propenoate (18). A mixture of compound **1** (288 mg, 1 mmol), 3-hydrazino-6-phenylpyridazine (**10**) (171 mg, 1 mmol), anhydrous ethanol (30 ml), and hydrochloric acid (37%, 3 drops, ~1 mmol) was stirred at room temperature for 4 h. The precipitate was collected by filtration, washed with anhydrous ethanol, and crystallized from methanol/water to give **18**. Yield 32% (136 mg); mp 214-216°C (from methanol water). IR, ν, cm^{-1}: 3450 (NH), 1750, 1720 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz), δ, ppm, *J* (Hz): major isomer **18**: 1.15 (3H, t, *J* = 7.0, $OCH_2C\underline{H}_3$); 4.05 (2H, q, *J* = 7.0, $OC\underline{H}_2CH_3$); 7.04 (1H, d, *J* = 9.4, 4'-H); 7.42-7.54 (3H, m, 3H of Ph); 7.75 (1H, d, *J* = 10.9, 3-H); 7.87-8.04 (6H, m, 4H of phthaloyl and 2H of Ph); 8.11 (1H, br d, *J* = 9.4, 5'-H); 9.50 (1H, d, *J* = 10.9, Het–NH–N<u>H</u>); 9.52 (1H, s, Het–N<u>H</u>–NH); minor isomer **18'**: 1.20 (3H, t, *J* = 7.0, $OCH_2C\underline{H}_3$); 4.22 (2H, q, *J* = 7.0, $OC\underline{H}_2CH_3$); 5.80 (1H, d, *J* = 4.5, 2-H); 7.11 (1H, d, *J* = 9.4, 4'-H); 7.84 (1H, d, *J* = 4.9, 3-H); 11.58 (s, 1H, Het–N<u>H</u>). Found, %: C 64.39; H 4.46; N 16.31. $C_{23}H_{19}N_5O_4$. Calculated, %: C 64.33; H 4.46; N 16.31.

General Procedure for the Preparation of Fused Pyrimidinones (20-22), Quinolizinones (25, 26), and Pyranones (35, 36). A mixture of compound **1** (288 mg, 1 mmol), ambident nucleophile **4**, **5**, **19**, **23**, **24**, **30**, **31** (1 mmol), sodium acetate (328 mg, 4 mmol), and acetic acid (100%, 3 ml) was heated under reflux for 3-24 h. The reaction mixture was cooled, the precipitate was collected by filtration, and washed with water and ethanol to give **20-22**, **25**, **26**, **35**, **36**. The following compounds were prepared in this manner:

6-(2,3-Dihydro-1,3-dioxo-1H-isoindol-2-yl)-5H-1,3-thiazolo[3,2-*a*]pyrimidin-5-one (20) was prepared from **1** and 2-amino-1,3-thiazole (**4**); refluxed for 24 h. Yield 15% (44 mg); mp 330-334°C (washed with hot methanol). IR, ν, cm^{-1}: 1720, 1690 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz), δ, ppm, *J* (Hz): 7.75 (1H, d, *J* = 4.9, 6-H); 7.94-8.04 (4H, m, phthaloyl); 8.18 (1H, d, *J* = 4.9, 7-H); 8.36 (s, 1H, 2-H). Found, %: C 56.73; H 2.35; N 13.81. $C_{14}H_7N_3O_3S$. Calculated, %: C 56.56; H 2.37; N 14.13.

3-(2,3-Dihydro-1,3-dioxo-1H-isoindol-2-yl)-4H-pyridino[1,2-*a*]pyrimidin-4-one (21) was prepared from **1** and 2-aminopyridine (**19**); refluxed for 13 h. Yield 29% (75 mg); mp 344-346°C (washed with hot methanol). IR, ν, cm^{-1}: 1720, 1690 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz), δ, ppm, *J* (Hz): 7.55 (1H, deg dt, *J* = 1.4; 6.9, 7-H); 7.90 (1H, dd, *J* = 1.4; 9.0, 9-H); 7.95-8.05 (4H, m, phthaloyl); 8.15 (1H, ddd, *J* = 1.6; 6.8; 8.9, 8-H); 8.60 (1H, s, 2-H); 9.07 (1H, dd, *J* = 1.6; 7.1, 6-H). Found, %: C 65.75; H 3.06; N 14.11. $C_{16}H_9N_3O_3$. Calculated, %: C 65.98; H 3.11; N 14.43.

3-(2,3-Dihydro-1,3-dioxo-1*H*-isoindol-2-yl)-8-methyl-4H-pyridino[1,2-*a*]pyrimidin-4-one (22) was prepared from **1** and 2-amino-4-methylpyridine (**5**); refluxed for 13 h. Yield 64% (196 mg); mp 325-327°C (washed with hot methanol). IR, ν, cm^{-1}: 1730, 1680 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz), δ, ppm, *J* (Hz): 2.55 (3H, s, 8-Me); 7.41 (1H, dd, *J* = 1.9, 7.2, 7-H); 7.72 (1H, d, *J* = 1.9, 9-H); 7.94-8.03 (4H, m, phthaloyl); 8.53 (1H, s, 2-H); 8.96 (1H, d, *J* = 7.2, 6-H). Found, %: C 66.88; H 3.50; N 13.46. $C_{17}H_{11}N_3O_3$. Calculated, %: C 66.88; H 3.63; N 13.76.

Ethyl 3-(2,3-Dihydro-1,3-dioxo-1H-isoindol-2-yl)-4-oxo-4H-quinolizine-1-carboxylate (25) was prepared from **1** and ethyl 2-pyridineacetate (**23**); refluxed for 5 h. Yield 58% (210 mg); mp 275-280°C (ethanol). IR, ν, cm^{-1}: 1720, 1680 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz), δ, ppm, *J* (Hz): 1.34 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 4.34 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 7.59 (1H, ddd, *J* = 1.3; 6.9; 7.1, 7-H); 7.97-8.54 (4H, m, phthaloyl); 8.11 (1H, ddd, *J* = 1.1; 6.7; 9.3, 8-H); 8.65 (1H, s, 2-H); 9.24-9.28 (2H, m, 6-H and 9-H). Found, %: C 66.08; H 3.86; N 7.56. $C_{20}H_{14}N_2O_5$. Calculated, %: C 66.30; H 3.89; N 7.73.

3-(2,3-Dihydro-1,3-dioxo-1H-isoindol-2-yl)-4-oxo-4H-quinolizine-1-carbonitrile (26) was prepared from **1** and 2-pyridineacetonitrile (**24**); refluxed for 5 h. Yield 62% (196 mg), mp 307-310 °C (from ethanol). IR, ν, cm^{-1}: 2360 (CN), 1720, 1680, 1650 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz), δ, ppm, *J* (Hz): 7.63 (1H, ddd, *J* = 1.8; 6.5; 8.1, 7-H); 7.95-8.05 (4H, m, phthaloyl); 8.09-8.17 (2H, m, 8-H and 9-H); 8.47 (1H, s, 2-H); 9.23 (1H, dd, *J* = 1.1; 8.0; 6-H). Found, %: C 68.58; H 2.69; N 13.09. $C_{18}H_9N_3O_3$. Calculated, %: C 68.57; H 2.88; N 13.33.

3-(2,3-Dihydro-1,3-dioxo-1H-isoindol-2-yl)-2H-pyrano[3,2-*c*]pyridin-2,5-(6H)-dione (35) was prepared from **1** and 4-dihydroxypyridin-2-one (**30**); refluxed for 6 h. Yield 54% (167 mg); mp >350°C (ethanol). IR, ν, cm^{-1}: 3450 (NH), 1750, 1720, 1650 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz), δ, ppm, *J* (Hz): 6.45 (1H, d, *J* = 7.3, 9-H); 7.77 (1H, d, *J* = 7.4, 8-H); 7.93-8.02 (4H, m, phthaloyl); 8.30 (1H, s, 4-H); 12.12 (1H, br. s, NH). Found, %: C 62.2; H 2.69; N 8.89. $C_{16}H_8N_2O_5$. Calculated, %: C 62.34; H 2.62; N 9.09.

3-(2,3-Dihydro-1,3-dioxo-1H-isoindol-2-yl)-7-methyl-2H,5H-pyrano[4,3-*b*]pyran-2,5-dione (36) was prepared from **1** and 4-hydroxy-6-methyl-2H-pyran-2-one (**31**); refluxed for 7 h. Yield 81% (262 mg); mp 297-300°C (ethanol). IR, ν, cm^{-1}: 1720 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz), δ, ppm, *J* (Hz): 2.37 (s, 3H, 7-Me); 6.75 (1H, s, 8-H); 7.92-8.02 (4H, m, phthaloyl); 8.23 (1H, s, 4-H). Found, %: C 63.55; H 2.86; N 4.22. $C_{17}H_9NO_6$. Calculated, %: C 63.16; H 2.81; N 4.33.

General Procedure for the Preparation of Pyranones (32-34). A mixture of compound **1** (288 mg, 1 mmol), ambident nucleophile **27-29** (1 mmol), sodium acetate (328 mg, 4 mmol), and acetic acid (100%, 6 ml) was heated under reflux for 2-3 h. Volatile components were evaporated in vacuo and ethanol (3 ml) was added to the residue. The precipitate was collected by filtration and washed with water and ethanol to give **32-34**. The following compounds were prepared in this manner:

Ethyl 3-(2,3-dihydro-1,3-dioxo-1H-isoindol-2-yl)-6-methyl-2-oxo-2H-pyran-5-carboxylate (32) was prepared from **1** and ethyl acetoacetate (**27**); refluxed for 3 h. Yield 46% (150 mg); mp 184-186°C (decomp.) (ethanol). ^{1}H NMR ($CDCl_3$, 300 MHz), δ, ppm, *J* (Hz): 1.35 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 2.78 (s, 3H, 6-Me); 4.36

(2H, q, J = 7.0, C<u>H</u>$_2$CH$_3$); 7.76-8.13 (4H, m, phthaloyl); 8.04 (1H, s, 4-H). Found, %: C 61.95; H 3.85; N 4.28. $C_{17}H_{13}NO_6$. Calculated, %: C 62.39; H 4.00; N 4.28.

3-(2,3-Dihydro-1,3-dioxo-1H-isoindol-2-yl)-5,6,7,8-tetrahydro-2H-1-benzopyran-2,5-dione (33) was prepared from **1** and cyclohexane-1,3-dione (**28**); refluxed for 2 h. Yield 57% (177 mg); mp 235-237.5°C (ethanol). ^{1}H NMR ($CDCl_3$, 300 MHz), δ, ppm, J (Hz): 2.0-3.1 (6H, m, 3 CH$_2$); 7.73-8.18 (4H, m, phthaloyl); 8.06 (1H, s, 4-H). Found, %: C 65.77; H 3.49; N 4.45. $C_{17}H_{11}NO_5$. Calculated, %: C 66.02; H 3.59; N 4.53.

3-(2,3-Dihydro-1,3-dioxo-1H-isoindol-2-yl)-7,7-dimethyl-5,6,7,8-tetrahydro-2H-1-benzopyran-2,5-dione (34) was prepared from **1** and 5,5-dimethyl-1,3-cyclohexanedione (**29**); refluxed for 3 h. Yield 56% (95 mg); mp 226-228.5°C (ethanol). ^{1}H NMR ($CDCl_3$, 300 MHz), δ, ppm, J (Hz): 1.20 (6H, s, 2 Me); 2.48 (s, 2H, CH$_2$); 2.82 (s, 2H, CH$_2$); 7.70-8.14 (4H, m, phthaloyl); 8.00 (1H, s, 4-H). Found, %: C 67.25; H 4.29; N 4.27. $C_{19}H_{15}NO_5$. Calculated, %: C 67.65; H 4.48; N 4.15.

Ethyl 2-(2,3-Dihydro-1,3-dioxo-1H-isoindol-2-yl)-3-(1,3-dioxo-2-cyclopentyl)propenoate Dimethylammonium Salt (39). A mixture of compound **1** (288 mg, 1 mmol), 1,3-cyclopentanedione (**37**) (98 mg, 1 mmol), and acetic acid (100%, 2 ml) was heated at 100°C for 2.5 h. Volatile components were evaporated in vacuo, the residue was triturated with ethanol (3 ml), and the precipitate was collected by filtration to give **39**. Yield 68% (263 mg); mp 215-223.5°C (decomp.) (ethanol). ^{1}H NMR (DMSO-d$_6$, 300 MHz), δ, ppm, J (Hz): 1.17 (3H, t, J = 7.1, OCH$_2$C<u>H</u>$_3$); 2.01 (4H, s, 2 CH$_2$); 2.57 (6H, s, NMe$_2$); 4.10 (2H, q, J = 7.1, OC<u>H</u>$_2$CH$_3$); 7.71 (s, 1H, 3-H); 7.87 (4H, s, phthaloyl). Found, %: C 62.01; H 5.61; N 7.22. $C_{20}H_{22}N_2O_6$. Calculated, %: C 62.17; H 4.74; N 7.25.

Ethyl 2-(2,3-Dihydro-1,3-dioxo-1H-isoindol-2-yl)-3-(1,3-dimethyl-2,4,6-trioxo-1H,3H,5H-pyrimidin-5-yl)propenoate Dimethylammonium Salt (40). A mixture of compound **1** (288 mg, 1 mmol), 1,3-dimethylbarbituric acid (**38**) (156 mg, 1 mmol), and acetic acid (100%, 3 ml) was heated at 80°C for 4 h. Volatile components were evaporated in vacuo, the residue was triturated with diethyl ether (5 ml), and the precipitate was collected by filtration to give **40**. Yield 91% (405 mg); mp 194-202°C (decomp.) (ethanol). ^{1}H NMR (DMSO-d$_6$, 300 MHz), δ, ppm, J (Hz): 1.15 (3H, t, J = 7.1, CH$_2$C<u>H</u>$_3$); 2.56 (s, 6H, NMe$_2$); 2.97 (6H, s, 1'-Me and 3'-Me); 4.07 (2H, q, J = 7.1, C<u>H</u>$_2$CH$_3$); 7.83 (4H, s, phthaloyl); 8.25 (s, 1H, 3-H). Found, %: C 56.42; H 5.29; N 12.39. $C_{21}H_{24}N_4O_7$. Calculated, %: C 56.75; H 5.44; N 12.61.

General Procedure for the Preparation of 3-Amino-4H-pyridino[1,2-*a*]pyrimidin-4-one (43) and Ethyl 3-Amino-4-oxo-4H-quinolizine-1-carboxylate (44). A mixture of compound **21** (146 mg, 0.5 mmol) or **25** (181 mg, 0.5 mmol), anhydrous ethanol (4 ml), and hydrazine hydrate (100%, 0.05 ml, 1 mmol) was heated at reflux temperature for 4 h. Volatile components were evaporated in vacuo and hydrochloric acid (10%, 5 ml) was added. The precipitate was collected by filtration to give phthalohydrazide **45** as the side product. The filtrate was neutralized with sodium hydrocarbonate, and the product was extracted with chloroform (3×15 ml). Organic phases were combined, dried over anhydrous sodium sulfate, filtered, and the filtrate was evaporated in vacuo to give **43** or **44**, respectively. The following compounds were prepared in this manner:

3-Amino-4H-pyridino[1,2-*a*]pyrimidin-4-one (43) was prepared from **21**. Yield 86% (69 mg), (lit. yield: 85% [12], 40-94% [13, 14]). Mp 174-178°C, (lit. mp 176-179°C [12]; 176-178°C [13, 14]).

Ethyl 3-Amino-4-oxo-4H-quinolizine-1-carboxylate (44) was prepared from **25**. Yield 28% (32 mg); lit. yield 94% [15]. Mp 136-141°C (lit. mp 136-139°C [15]).

X-ray Structural Analysis. Diffraction data for compound **1** were collected on an Enraf-Nonius CAD4 diffractometer using graphite monochromated MoKα radiation. Structure was solved by direct methods using the MULTAN88 [16] program. The Xtal3.4 [17] system of crystallographic programs was used for the correlation and reduction of data, structure refinement, and interpretation. ORTEPII [18] was used to produce molecular graphics. The resulting crystal data and details concerning data collection and refinement are quoted in Table 1. Bond lengths and angles are presented in the Tables 2, 3. The crystallographic data for compound **2** have also been deposited with the Cambridge Crystallographic Data Centre as supplementary material with deposition number CCDC 167581. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.

The asymmetric unit of compound **1** is shown in Fig. 1. It contains two molecules of (*Z*)-2-(2,3-dihydro-1,3-dioxo-1H-isoindol-2-yl)-3-(dimethylamino)propenoate (**1**).

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