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v-Triazolines. Part 42.[1] Study on the reactivity of 4,5-dihydro-1-(6-methyl-2-oxo-2*H*-pyran-4-yl)-5-morpholino-*v*-triazoles. Synthetic approach to pyrano[4,3-*b*]pyrrol-4(1*H*)-ones

Emanuela Erba, Donato Pocar and Pasqualina Trimarco *

Istituto di Chimica Organica, Facoltà di Farmacia e Centro Interuniversitario di Ricerca
sulle Reazioni Pericicliche e Sintesi di Sistemi Etero e Carbociclici, Università di Milano,
Via Venezian 21, I-20133 Milano, Italy. E-mail: trimarco@mailserver.unimi.it

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Pyrolysis of 4-aryl-5-morpholino-4,5-dihydrotriazoles **3** affords two products: pyrano[4,3-*b*]pyrrol-4(1*H*)-ones **4** and arylacetamidines **5**. The reaction mechanism of this transformation is discussed and reaction conditions optimized to enhance the formation of pyrrole-fused pyran-2-one derivatives **4**. 2-Aminoaziridines are considered to be key intermediates in this transformation.

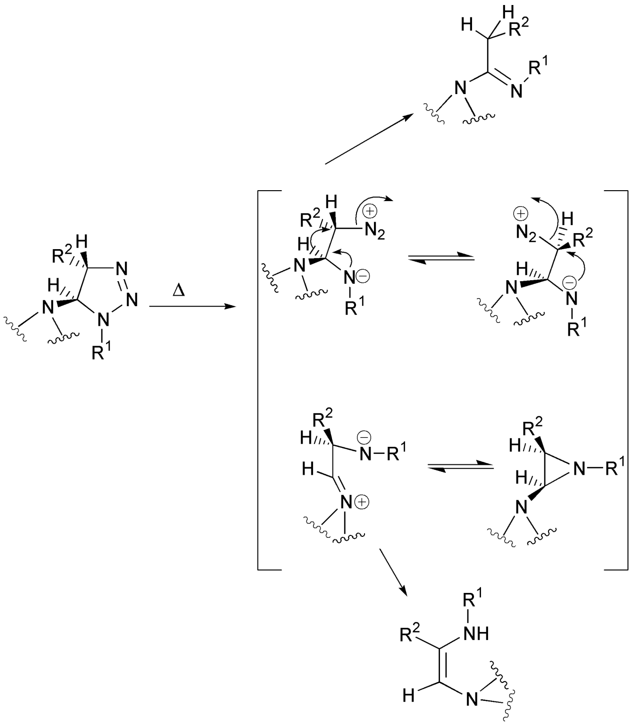
2*H*-Pyran-2-ones are of interest as synthons for organic synthesis, particularly since many derivatives, isolated from natural sources, exhibit remarkable biological properties.[2] Renewed interest comes from the discovery of a new type of non-peptidic HIV-protease inhibitor containing this nucleus.[3]

In 2*H*-pyranones the C-3 position is nucleophilic, presenting the characteristic reactivity of enols, and electrophiles react at C-3 with conservation of the pyrone ring.[4]

Our research group has been studying transformations and uses of 5-amino-4,5-dihydro-*v*-triazoles, mainly as precursors of substituted amidines, synthons from which N-heterocycles can be derived.[5] It is well known that 5-amino-4,5-dihydro-*v*-triazoles readily aromatize to triazoles[6a] by heat or under the action of acid or base by elimination of a molecule of amine. The 5-amino-4,5-dihydro-*v*-triazoles give rise to amidines when the R group on N-1 is highly electron withdrawing and the 5-amino group is tertiary.[6b] In a previous paper[7] we pointed out that thermolysis can induce 4,5-dihydro-*v*-triazole ring cleavage (Scheme 1). The zwitterionic intermediate, produced by ring–chain tautomerism of the triazoline ring, undergoes two different reactions: direct formation of the amidine by N_2 loss and simultaneous hydride transfer, or alternatively ring contraction into the 2-aminoaziridine, associated with N_2 loss. We also observed the formation of labile diaminoethylenic derivatives, whose formation has been rationalized by invoking the presence of an aziridine intermediate. Cleavage of the aziridine bond between N and the C atom bearing the amino residue, through its iminium form, explained the ethylenic intermediates.

These results prompted us to synthesize 5-amino-4,5-dihydro-*v*-triazoles bearing a 2*H*-pyran-2-one group at N-1, and to explore the possibility of linking both the reactivity of 2-aminoaziridines and the nucleophilic features of C-3 in the 2*H*-pyran-2-one nucleus.

Suitable conditions were sought to achieve transformation of the intermediate aminoaziridine pyrrole-fused pyran-2-one derivatives. Little chemistry of this ring system has been investigated[8] although some substituted derivatives have been prepared from pyrrol-2-ylacetic acid derivatives[9] by a multistep sequence. A synthetic pathway involving 5-amino-4,5-dihydro-*v*-triazoles has never been described.



Scheme 1

Results and discussion

4,5-Dihydro-*v*-triazoles **3a–d**,**f**,**g** were easily obtained from cycloaddition of azide **1** and appropriate enamines **2a–d**,**f**,**g** in benzene while **3e** was prepared by one-pot procedure[10] from propionaldehyde, 4-azido-6-methyl-2*H*-pyran-2-one **1** and morpholine without isolation of the intermediate enamine **2e** (Scheme 2). Satisfactory yields were obtained and the structures of products, including their *trans* configuration,[11] were established from ^{1}H NMR data (see Experimental section).

Compounds **3a–g** were thermolyzed by heating them in boiling toluene until complete consumption of the starting

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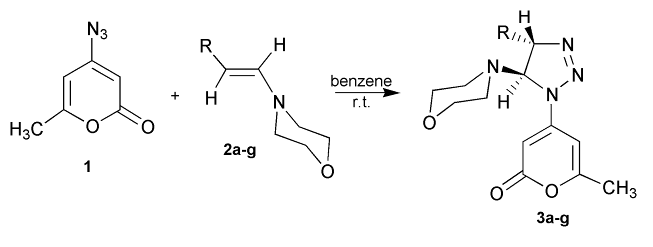
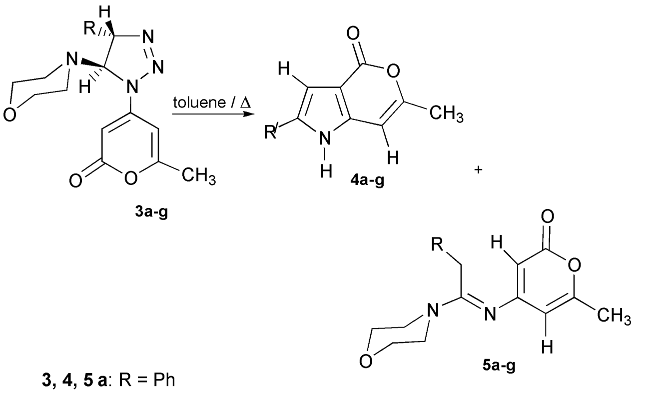


2,3 a: R = Ph
b: R = 4-MeC$_6$H$_4$
c: R = 4-MeOC$_6$H$_4$
d: R = 4-ClC$_6$H$_4$
e: R = Me^a
f: R = 4-BrC$_6$H$_4$
g: R = 4-FC$_6$H$_4$

Scheme 2 ^{a} **2e** not isolated, but obtained *in situ*: see Experimental section, preparation of compound **3e**.

compound (about 1–2 hours). Starting from **3a–d**,**f**,**g** a mixture of pyrrole-fused pyran-2-ones **4a–d**,**f**,**g** and amidines **5a–d**,**f**,**g**, respectively, was formed. Dihydro-*v*-triazole **3e** gave only amidine **5e** (Scheme 3).



3, 4, 5 a: R = Ph
b: R = 4-MeC$_6$H$_4$
c: R = 4-MeOC$_6$H$_4$
d: R = 4-ClC$_6$H$_4$
e: R = Me^a
f: R = 4-BrC$_6$H$_4$
g: R = 4-FC$_6$H$_4$

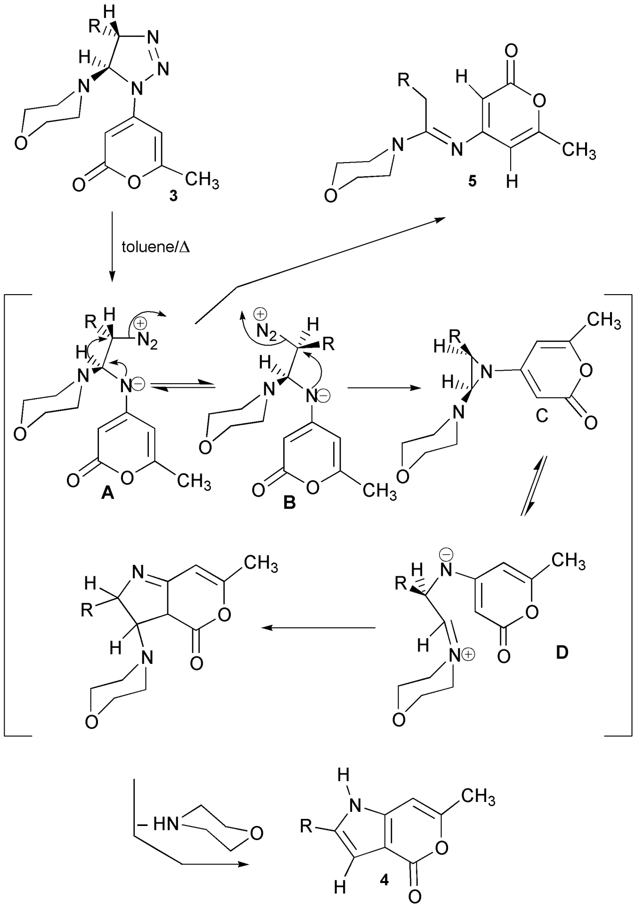
Scheme 3 ^{a} **4e** was obtained in toluene but only in the presence of BF$_3$·Et$_2$O (Tables 1 and 2).

Spectroscopic data established the structure of tertiary amidines **5a–g** and of 2-aryl-6-methylpyrano[4,3-*b*]pyrrol-4(1*H*)-ones **4a–d**,**f**,**g**. Assignment of protons and carbons in ^{1}H and ^{13}C spectra of amidines **5a–g** was made on the basis of HETCOR and COLOC experiments, and data related to the pyran-2-one nucleus were in agreement with the literature.[12] All amidines **5** (in CDCl$_3$) show a typical pattern for the signal of the C-3 proton in the range δ 5.15–5.29 and for the C-5 proton in the range δ 5.58–5.66. A NOESY experiment, performed for amidine **5a**, demonstrated correlation between the singlet at δ 3.8 (CH$_2$Ph) and the singlet at δ 5.29 (pyran-2-one 3-H), supporting the assigned (*E*) configuration of the amidine double bond.

All pyrano[4,3-*b*]pyrrol-4-ones **4a–d**,**f**,**g** show typical proton signals (in DMSO-d$_6$) due to the C-7 and C-3 protons at $\delta \approx 6.5$ and δ 6.87–7.07, respectively. The complete assignment of the peaks in the ^{13}C NMR spectrum was facilitated by 2D NMR spectroscopy performed on the pyrano[4,3-*b*]pyrrol-4(1*H*)-one **4a**: HETCOR experiments allowed attribution of the CH-7 signals (δ 6.48 and δ_C 96) as well as the CH-3 signal (δ 7.01 and $\delta_C \approx 103$), quaternary carbons being assigned from the results of a COLOC experiment. For all compounds **4** proton/carbon resonances are reported in the Experimental section.

Conclusive structural assignment of compounds **4a–d**,**f**,**g** was obtained by NOESY experiments (DMSO-d$_6$) on **4a**, which displayed clear correlations between H-7 and the CH$_3$ linked to C-6. A positive Overhauser effect confirmed also the spatial proximity of the NH group to H-7 as well as to the *ortho* hydrogens of the C-2 phenyl group.

The formation of amidines **5** is expected[6b] according to the general rearrangement path of 5-amino-4,5-dihydrotriazoles as indicated in Scheme 1. The production of fused heterocycles **4** can be rationalized as occurring *via* aminoaziridine **C** (Scheme 4). The previously observed[7] bond cleavage between the N atom and the C atom linked to the morpholine residue forms **D**, where nucleophilic attack of C-3 of the pyran-2-one on the iminium carbon occurs to give a dihydropyrano[4,3-*b*]pyrrol-4-one intermediate, which, by amine loss, turns into the corresponding pyrano[4,3-*b*]pyrrol-4(1*H*)-one **4**.



Scheme 4

The reaction was studied in more detail, both to confirm that bicycles **4** do not arise from the amidines **5**, and to determine those factors that would enhance the yield of the pyrrole-fused pyran-2-ones **4**. In a first experiment amidine **5a** was refluxed in toluene for 60 min, under the same conditions adopted for the decomposition of 4,5-dihydro-*v*-triazole **3a**. The ^{1}H NMR spectrum of the crude mixture showed only the signals of amidine **5a**, thus confirming the independence of paths leading to **4** and **5**, respectively.

In order to increase the yield of compounds **4**, 4,5-dihydro-*v*-triazoles **3a–g** were treated under two different conditions: i) refluxing in propan-1-ol until disappearance of starting material was complete; ii) boiling in dry toluene with an equimolar amount of BF$_3$·Et$_2$O for the same time. Propan-1-ol was selected on account of its suitable boiling point. It was

Table 1 Ratios of **4** and **5** estimated by ^{1}H NMR spectroscopy

Compound **3**	Toluene	Pr^{n}OH	Toluene, BF$_3$·Et$_2$O
3a	**4a** : **5a** (33 : 67)	**4a** : **5a** (18 : 82)	**4a** : **5a** (70 : 30)
3b	**4b** : **5b** (38 : 62)	**4b** : **5b** (34 : 66)	**4b** : **5b** (88 : 12)
3c	**4c** : **5c** (37 : 63)	**4c** : **5c** (66 : 34)	**4c** : **5c** (82 : 18)
3d	**4d** : **5d** (44 : 56)	**4d** : **5d** (19 : 81)	**4d** : **5d** (94 : 6)
3e	**4e** : **5e** (0 : 100)	**4e** : **5e** (0 : 100)	**4e** : **5e** (25 : 75)
3f	**4f** : **5f** (48 : 52)	**4f** : **5f** (28 : 72)	**4f** : **5f** (83 : 17)
3g	**4g** : **5g** (32 : 68)	**4g** : **5g** (22 : 78)	**4g** : **5g** (63 : 37)

expected that this polar and protic solvent might influence the equilibrium between the conformers **A** and **B** previously seen in Scheme 1. In this reaction setting we were expecting the dipolar form **A** to prevail and, from N_2 loss, the amount of amidines **5** to increase.

Dry toluene and BF$_3$·Et$_2$O were used in attempts to stabilize the iminium intermediate **D** in Scheme 4. It is well known that aziridines with electron-withdrawing groups,[13] such as alkylsulfonyl, acyl, alkoxycarbonyl, and in our case the unsaturated lactone pyran-2-one linked to the N atom, conjugatively stabilize the negative charge that develops on the nitrogen in the ring-opening transition state. In this context (see Scheme 4) BF$_3$ could bond to the anionic nitrogen, in iminium form **D**, or conjugatively to the enolate oxygen atom and hence promote the formation of **4**. Table 1 collects the results obtained under three different conditions. The ratio **4** : **5** in the product mixture was determined by ^{1}H NMR analysis.

The data of Table 1 confirm the correctness of the above choices and give support to the formulated mechanistic hypothesis, that the achievement of heterocycles **4** and the amidines **5** comes from two competitive pathways. An effective increase in the yield of amidines **5** was seen when the reaction was performed propan-1-ol, while the addition of the Lewis acid catalyst brought about an increase of the yield of pyrrole-fused pyran-2-one derivatives **4**, suggesting that the participation of polar solvents and/or complexing catalyst can act on the equilibrium between **A** and **B**, favouring the hydride transfer or the formation of the aziridine intermediate.

In conclusion, variations in the reaction medium controlled the transformation of 4,5-dihydro-*v*-triazoles **3** and facilitated our aim of linking the reactivity of 2-aminoaziridines and the nucleophilic reactivity of C-3 in the 2*H*-pyranone nucleus.

Experimental

Mps were determined using a Büchi 510 (capillary) or an Electrothermal 9100 apparatus and are uncorrected. IR spectra were measured using a JASCO IR Report 100 instrument. ^{1}H and ^{13}C NMR spectra (tetramethylsilane as internal standard) were recorded with EM Varian Gemini 200, Bruker AC 200 and Bruker Avance 300 Spectrometers. *J*-Values are given in Hz for solutions in CDCl$_3$ or DMSO-d_6. Mass spectral data were obtained on a Varian MAT 1H COS 50 instrument using electron-impact ionization techniques at 70 eV. Column chromatography was performed on Kieselgel 60 (Merck), 0.063–0.200 mm, and elution with cyclohexane–ethyl acetate (ratios indicated in Experimental section).

Materials

Azide **1**[14] and enamines **2a–c**,[15] **2f**,[15] **2d**,[16] **2g**[17] have already been described.

4,5-Dihydro-1-(6-methyl-2-oxo-2*H*-pyran-4-yl)-5-morpholino-1,2,3-triazoles 3a–d,f,g

Typical procedure. Azide **1** (3.0 g, 20 mmol) was dissolved in benzene (20 ml) and an equimolar amount of an enamine **2a**, **b**, **d**, **f**, **g**, dissolved in benzene (20 ml), was added under stirring at room temperature. Enamine **2c** solution in benzene was added dropwise to the stirred azide solution at 0–5 °C. As soon as the starting azide had disappeared (TLC, cyclohexane–ethyl acetate 3 : 7), the solvent was removed under reduced pressure and the crude product was crystallized from an appropriate solvent.

4-(4,5-Dihydro-5-morpholino-4-phenyl-1*H*-1,2,3-triazol-1-yl)-6-methyl-2*H*-pyran-2-one 3a. Reaction time 2 h; yield 6.5 g (96%); white plates from Pr$^i{}_2$O; mp 85 °C (decomp.); IR (Nujol) ν_{max} 1700 (C=O) cm^{-1}; ^{1}H NMR (200 MHz; CDCl$_3$) δ 2.30 (3H, s, Me), 2.39–2.47 (4H, m, CH$_2$NCH$_2$), 3.64–3.72 (4H, m, CH$_2$OCH$_2$), 4.62 (1H, d, *J* 3.4, 5-H), 5.61 (1H, d, *J* 3.4, 4-H), 5.72 (1H, s, 3-H pyranone), 6.78 (1H, s, 5-H pyranone), 6.95–7.42 (5H, m, ArH) (Calc. for $C_{18}H_{20}N_4O_3$: C, 63.52; H, 5.92; N, 16.46. Found: C, 63.69; H, 6.03; N, 16.18%).

4-(4,5-Dihydro-5-morpholino-4-*p*-tolyl-4-1*H*-1,2,3-triazol-1-yl)-6-methyl-2*H*-pyran-2-one 3b. Reaction time 2 h; yield 5.7 g (81%); white plates from Pr$^i{}_2$O; mp 108 °C (decomp.); IR (Nujol) ν_{max} 1700 (C=O) cm^{-1}; ^{1}H NMR (200 MHz; CDCl$_3$) δ 2.29 (3H, s, Me), 2.33 (3H, s, *p*-tolyl), 2.35–2.44 (4H, m, CH$_2$NCH$_2$), 3.63–3.69 (4H, m, CH$_2$OCH$_2$), 4.58 (1H, d, *J* 3.4, 5-H), 5.57 (1H, d, *J* 3.4, 4-H), 5.71 (1H, s, 3-H pyranone), 6.78 (1H, s, 5-H pyranone), 6.87 and 7.17 (4H, dd, AB system, *J* 8.0, ArH (Calc. for $C_{19}H_{22}N_4O_3$: C, 64.39; H, 6.26; N, 15.81. Found: C, 64.6; H, 6.31; N, 15.55%).

4-[4,5-Dihydro-4-(4-Methoxyphenyl)-5-morpholino-1*H*-1,2,3-triazol-1-yl]-6-methyl-2*H*-pyran-2-one 3c. Reaction time 2 h; yield 4.7 g (64%); white plates from Pr$^i{}_2$O; mp 65–66 °C (decomp.); IR (Nujol) ν_{max} 1700 (C=O) cm^{-1}; ^{1}H NMR (200 MHz; CDCl$_3$) δ 2.30 (3H, s, Me), 2.38–2.47 (4H, m, CH$_2$NCH$_2$), 3.63–3.70 (4H, m, CH$_2$OCH$_2$), 3.80 (3H, s, OMe), 4.58 (1H, d, *J* 3.4, 5-H), 5.56 (1H, d, *J* 3.4, 4-H), 5.71 (1H, s, 3-H pyranone), 6.79 (1H, s, 5-H pyranone), 6.88–6.98 (4H, m, ArH) (Calc. for $C_{19}H_{22}N_4O_4$: C, 61.61; H, 5.99; N, 15.13. Found: C, 61.84; H, 6.12; N, 14.97%).

4-[4-(4-Chlorophenyl)-4,5-dihydro-5-morpholino-1*H*-1,2,3-triazol-1-yl]-6-methyl-2*H*-pyran-2-one 3d. Reaction time 24 h; yield 5.5 g (73%); white plates from benzene; mp 107 °C (decomp.); IR (Nujol) ν_{max} 1700 (C=O) cm^{-1}; ^{1}H NMR (200 MHz; CDCl$_3$) δ 2.30 (3H, s, Me), 2.38–2.48 (4H, m, CH$_2$NCH$_2$), 3.64–3.75 (4H, m, CH$_2$OCH$_2$), 4.58 (1H, d, *J* 3.5, 5-H), 5.58 (1H, d, *J* 3.5, 4-H), 5.71 (1H, s, 3-H pyranone), 6.75 (1H, s, 5-H pyranone), 6.94 and 7.36 (4H, dd, AB system, *J* 8.5, ArH) (Calc. for $C_{18}H_{19}ClN_4O_3$: C, 57.68; H, 5.11; N, 14.95. Found: C, 57.89; H, 5.18; N, 14.68%).

4-[4-(4-Bromophenyl)-4,5-dihydro-5-morpholino-1*H*-1,2,3-triazol-1-yl]-6-methyl-2*H*-pyran-2-one 3f. Reaction time 2 h; yield 5.4 g (64%); cream plates from ethanol; mp 115 °C (decomp.); IR (Nujol) ν_{max} 1700 (C=O) cm^{-1}; ^{1}H NMR (200 MHz; CDCl$_3$) δ 2.32 (3H, s, Me), 2.36–2.47 (4H, m, CH$_2$NCH$_2$), 3.64–3.75 (4H, m, CH$_2$OCH$_2$), 4.60 (1H, d, *J* 3.6, 5-H), 5.58 (1H, d, *J* 3.6, 4-H), 5.73 (1H, s, 3-H pyranone), 6.79 (1H, s, 5-H pyranone), 6.89 and 7.53 (4H, dd, AB system, *J* 8.4, ArH) (Calc. for $C_{18}H_{19}BrN_4O_3$: C, 51.56; H, 4.57; N, 13.36. Found: C, 51.63; H, 4.81; N, 13.07%).

4-[4-(4-Fluorophenyl)-4,5-dihydro-5-morpholino-1*H*-1,2,3-triazol-1-yl]-6-methyl-2*H*-pyran-2-one 3g. Reaction time 3 h; yield 4.1 g (57%); cream plates from ethanol; mp 118 °C (decomp.); IR (Nujol) ν_{max} 1690 (C=O) cm^{-1}; ^{1}H NMR (200 MHz; CDCl$_3$) δ 2.33 (3H, s, Me), 2.40–2.47 (4H, m, CH$_2$NCH$_2$), 3.68–3.75 (4H, m, CH$_2$OCH$_2$), 4.60 (1H, d, *J* 3.6, 5-H), 5.60 (1H, d, *J* 3.6, 4-H), 5.74 (1H, s, 3-H pyranone), 6.80 (1H, s, 5-H pyranone), 6.90–7.16 (4H, m, ArH) (Calc. for

Table 2 Preparation of pyranol[4,3-*b*]pyrrol-4(1*H*)-ones **4** or amidines **5** from 5-amino-4,5-dihydro-*v*-triazoles **3**

Entry	R	Method[a]	Reaction time (*t*/min)	*T*/°C	Yield of isolated products (%)
3a	Ph	A	60	111	**4a** (21) **5a** (55)
3a	Ph	B	120	97	**4a** (13) **5a** (70)
3a	Ph	C	60	111	**4a** (58) **5a** (18)
3b	4-MeC_6H_4	A	90	111	**4b** (24) **5b** (46)
3b	4-MeC_6H_4	B	90	97	**4b** (22) **5b** (56)
3b	4-MeC_6H_4	C	90	111	**4b** (77) **5b** (7)
3c	4-$MeOC_6H_4$	A	90	111	**4c** (25) **5c** (48)
3c	4-$MeOC_6H_4$	B	120	97	**4c** (53) **5c** (20)
3c	4-$MeOC_6H_4$	C	90	111	**4c** (70) **5c** (13)
3d	4-ClC_6H_4	A	100	111	**4d** (36) **5d** (47)
3d	4-ClC_6H_4	B	80	97	**4d** (11) **5d** (68)
3d	4-ClC_6H_4	C	120	111	**4d** (88) **5d** (2)
3e	Me	A	120	111	**5e** (86)
3e	Me	B	120	97	**5e** (88)
3e	Me	C	120	111	**4e** (16) **5e** (58)
3f	4-BrC_6H_4	A	120	111	**4f** (36) **5f** (43)
3f	4-BrC_6H_4	B	120	97	**4f** (15) **5f** (60)
3f	4-BrC_6H_4	C	120	111	**4f** (65) **5f** (10)
3g	4-FC_6H_4	A	120	111	**4g** (22) **5g** (56)
3g	4-FC_6H_4	B	120	97	**4g** (13) **5g** (64)
3g	4-FC_6H_4	C	120	111	**4g** (45) **5g** (30)

[a] Solvents: A, toluene; B, propan-1-ol; C, toluene, $BF_3{\cdot}Et_2O$.

$C_{18}H_{19}FN_4O_3$: C, 60.33; H, 5.34; N, 15.63. Found: C, 60.46; H, 5.41; N, 15.35%).

Preparation of 4-(4,5-dihydro-4-methyl-5-morpholino-1*H*-1,2,3-triazol-1-yl)-6-methyl-2*H*-pyran-2-one 3e

A benzene solution (30 ml) of morpholine (2.61 g, 30 mmol) was added dropwise to a stirred solution of azide **1** (4.5 g, 30 mmol) and propanal (1.74 g, 30 mmol) in benzene (30 ml) at rt until the starting azide had disappeared (*ca.* 20 h) (TLC cyclohexane–EtOAc, 1 : 9). The solution was dried with Na_2SO_4, filtered, and the filtrate was evaporated under reduced pressure. The residue was crystallized from Pr^i_2O to afford pure **3e**. (5.6 g, 67%), as white needles; mp 113 °C (decomp.); IR (Nujol) ν_{max} 1700 (C=O) cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$) δ 1.28 (3H, d, *J* 7.2, 4-Me triazoline), 2.28 (3H, s, Me), 2.30–2.38 (4H, m, CH_2NCH_2), 3.61–3.68 (4H, m, CH_2OCH_2), 4.31 (1H, d, *J* 3.1, 5-H), 4.58 (1H, dq, *J* 3.1 and 7.2, 4-H), 5.70 (1H, s, 3-H pyranone), 6.72 (1H, s, 5-H pyranone) (Calc. for $C_{13}H_{18}N_4O_3$: C, 56.10; H, 6.52; N, 20.13. Found: C, 56.22; H, 6.64; N, 20.01%).

Thermal behaviour of dihydrotriazoles 3a–g. Method A

Typical procedure for the synthesis of compounds 4a–d,f,g and 5a–g. Dihydrotriazoles **3a**–**g** (15 mmol) dissolved in toluene (70 ml) were heated under reflux for times indicated in Table 2, progress of the reaction being followed by TLC. After disappearance of the starting material the solvent was removed *in vacuo* and a small amount of the residue was dissolved in DMSO-d_6 and the ratio of **4** to **5** was determined by ^1H NMR analysis (see Table 1). The crude residue was taken up with CH_2Cl_2 and slowly and partially deposited a compound **4a**–**d**,**f**,**g** as a crystalline product, which was filtered off and recrystallized as indicated below. The left over mixture was chromatographed (cyclohexane–ethyl acetate 3 : 7) to give a first fraction containing a pyrano[4,3-*b*]pyrrol-4-one **4a**–**d**,**f**,**g** and a second fraction containing an amidine **5a**–**d**,**f**,**g**. Dihydrotriazole **3e** afforded only amidine **5e**, isolated by crystallization from Pr^i_2O. Pyrrole-fused pyran-2-one **4e** was isolated only from reaction with $BF_3{\cdot}Et_2O$ (see below). Reaction times of dihydrotriazoles **3** and yields of isolated products **4** and **5** are collected in Table 2.

6-Methyl-2-phenylpyrano[4,3-b]pyrrol-4(1H)-one **4a**. White plates from Pr^i_2O; mp 223 °C; IR (Nujol) ν_{max} 3250 (NH), 1675 (C=O) cm^{-1}; ^1H NMR (300 MHz; DMSO-d_6) δ 2.26 (3H, s, Me), 6.48 (1H, s, 7-H), 7.01 (1H, s, 3-H), 7.19–7.82 (5H, m, ArH), 12.2 (1H, br s, NH exchangeable); ^{13}C NMR (75 MHz; DMSO-d_6) δ 20.2 (Me), 96.0 (C-7), 103.2 (C-3), 108.3 (C-3a), 125.3, 128.1, 129.7 (ArCH), 131.9 (ArC), 135.98 (C-2), 141.4 (C-7a), 156.5 (C-6), 160.4 (C=O); MS *m*/*z* 225 (M^+, 100%), 197 (35) (Calc. for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.39; H, 5.01; N, 6.12%).

6-Methyl-4-(1-morpholino-2-phenylethylideneamino)-2H-pyran-2-one **5a**. White plates from Pr^i_2O; mp 135 °C; IR (Nujol) ν_{max} 1705 (C=O) cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ 2.15 (3H, s, Me), 3.45–3.47 (8H, 2m, morpholino), 3.80 (2H, s, CH_2), 5.29 (1H, d, *J* 1.7, 3-H), 5.66 (1H, d, *J* 1.7, 5-H), 7.10–7.38 (5H, m, ArH); ^{13}C NMR (75 MHz; $CDCl_3$) δ 20.3 (Me), 34.7 (CH_2), 45.8 (CH_2NCH_2), 66.8 (CH_2OCH_2), 96.4 (C-3), 105.0 (C-5), 127.6, 128.0, 129.6 (ArCH), 135.3 (ArC), 156.8 (N-C=N), 161.8 (C-6), 165.1 (C-4), 165.4 (C=O) (Calc. for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.33; H, 6.53; N, 8.88%).

6-Methyl-2-p-tolylpyrano[4,3-b]pyrrol-4(1H)-one **4b**. White plates from Pr^i_2O; mp 268 °C; IR (Nujol) ν_{max} 3150 (NH), 1680 (C=O) cm^{-1}; ^1H NMR (200 MHz; DMSO-d_6) δ 2.27 (3H, s, Me), 2.32 (3H, s, *p*-tolyl), 6.48 (1H, s, 7-H), 6.93 (1H, s, 3-H), 7.24 and 7.66 (4H, dd, AB system, *J* 8.4, ArH), 12.10 (1H, br s, NH exchangeable); ^{13}C NMR (50 MHz; DMSO-d_6) δ 19.6 (Me), 20.9 (Me), 95.4 (C-7), 101.8 (C-3), 107.7 (C-3a), 124.6, 129.7 (ArCH), 128.6 (ArC), 135.5 (C-2), 136.9 (ArC), 140.6 (C-7a), 155.6 (C-6), 159.8 (C=O) (Calc. for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.06; H, 5.57; N, 5.63%).

6-Methyl-4-(1-morpholino-2-p-tolylethylideneamino)-2H-pyran-2-one **5b**. White plates from Pr^i_2O; mp 191 °C; IR (Nujol) ν_{max} 1700 (C=O) cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$) δ 2.15 (3H, s, Me), 2.32 (3H, s, *p*-tolyl), 3.44–3.57 (8H, m, morpholine), 3.74 (2H, s, CH_2), 5.28 (1H, s, 3-H), 5.65 (1H, s, 5-H), 6.99 and 7.12 (4H, dd, AB system, *J* 8.4, ArH); ^{13}C (50 MHz; $CDCl_3$) δ 19.9 (Me), 21.0 (Me), 33.9 (CH_2), 45.4 (CH_2NCH_2), 66.5 (CH_2OCH_2), 96.2 (C-3), 104.7 (C-5), 127.5, 129.9 (ArCH), 131.8 (ArC), 136.8 (ArC), 156.6 (N-C=N), 161.4 (C-6), 164.8 (C-4), 165.0 (C=O) (Calc. for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58. Found: C, 70.20; H, 6.72; N, 8.45%).

2-(4-Methoxyphenyl)-6-methylpyrano[4,3-b]pyrrol-4(1H)-one **4c**. Cream plates from CH_2Cl_2; mp 242 °C; IR (Nujol) ν_{max} 3230 (NH), 1670 (C=O) cm^{-1}; ^1H NMR (200 MHz; DMSO-d_6)

δ 2.28 (3H, s, Me), 3.80 (3H, s, OMe), 6.48 (1H, s, 7-H), 6.87 (1H, s, 3-H), 7.02 and 7.71 (4H, dd, AB system, *J* 8.7, ArH), 12.05 (1H, br s, NH exchangeable); ^{13}C NMR (50 MHz; DMSO-d_6) δ 19.6 (Me), 55.4 (OMe), 95.4 (C-7), 101.1 (C-3), 107.7 (C-3a), 114.6, 126.1 (ArCH), 124.2 (ArC), 135.5 (C-2), 140.49 (C-7a), 155.5 (C-6), 158.9 (OMe), 159.9 (C=O) (Calc. for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.37; H, 4.96; N, 5.35%).

*4-[2-(4-Methoxyphenyl)-1-morpholinoethylideneamino]-6-methyl-2H-pyran-2-one **5c***. Orange plates from Pr^i_2O; mp 106 °C; IR (Nujol) ν_{max} 1700 (C=O) cm^{-1}; ^{1}H NMR (200 MHz; $CDCl_3$) δ 2.16 (3H, s, Me), 3.40–3.50 (4H, m, CH_2NCH_2), 3.50–3.60 (4H, m, CH_2OCH_2), 3.72 (2H, s, CH_2), 3.80 (3H, s, OMe), 5.28 (1H, s, 3-H), 5.65 (1H, s, 5-H), 6.85 and 7.03 (4H, dd, AB system, *J* 8.7, ArH) (Calc. for $C_{19}H_{22}N_2O_4$: C, 66.65; H, 6.48; N, 8.18. Found: C, 66.88; H, 6.71; N, 6.22%).

*2-(4-Chlorophenyl)-6-methylpyrano[4,3-b]pyrrol-4(1H)-one **4d***. White plates from. CH_2Cl_2; mp 291 °C; IR (Nujol) ν_{max} 3230 (NH), 1670 (C=O) cm^{-1}; ^{1}H NMR (200 MHz; DMSO-d_6) δ 2.28 (3H, s, Me), 6.50 (1H, s, 7-H), 7.07 (1H, s, 3-H), 7.50 and 7.80 (4H, dd, AB system, *J* 8.5, ArH), 12.22 (1H, br s, NH exchangeable); ^{13}C NMR (50 MHz; DMSO-d_6) δ 19.6 (Me), 95.3 (C-7), 103.3 (C-3), 107.8 (C-3a), 126.3, 129.1 (ArCH), 130.3 and 131.9 (2 × ArC), 134.2 (C-2), 141.0 (C-7a), 156.1 (C-6), 159.7 (C=O) (Calc. for $C_{14}H_{10}ClNO_2$: C, 64.75; H, 3.88; N, 5.39. Found: C, 64.54; H, 3.83; N, 5.31%).

*4-[2-(4-Chlorophenyl)-1-morpholinoethylideneamino]-6-methyl-2H-pyran-2-one **5d***. Pale yellow plates from MeOH; mp 158 °C; IR (Nujol) ν_{max} 1690 (C=O) cm^{-1}; ^{1}H NMR (200 MHz; $CDCl_3$) δ 2.16 (3H, s, Me), 3.38–3.50 (4H, m, CH_2NCH_2), 3.50–3.63 (4H, m, CH_2OCH_2), 3.76 (2H, s, CH_2), 5.24 (1H, s, 3-H), 5.64 (1H, s, 5-H), 7.06 and 7.31 (4H, dd, AB system, *J* 8.4, ArH) (Calc. for $C_{18}H_{19}ClN_2O_3$: C, 62.34; H, 5.52; N, 8.08. Found: C, 62.08; H, 5.43; N, 7.95%).

*6-Methyl-4-(1-morpholinopropylideneamino)-2H-pyran-2-one **5e***. White plates from Pr^i_2O; mp 85–86 °C; IR (Nujol) ν_{max} 1700 (C=O) cm^{-1}; ^{1}H NMR (200 MHz; $CDCl_3$) δ 1.11 (3H, t, *J* 7.6, Me), 2.19 (3H, s, pyranone-Me), 2.36 (2H, dd, *J* 7.6, CH_2), 3.45–3.51 and 3.70–3.76 (8H, 2m, morpholine), 5.24 (1H, d, *J* 1.7, 3-H), 5.62 (1H, d, *J* 1.7, 5-H); ^{13}C NMR (50 MHz; DMSO-d_6) δ 12.4 (Me linked to CH_2), 19.6 (6-Me), 21.7 (CH_2), 45.2 (CH_2NCH_2), 66.2 (CH_2OCH_2), 95.0 (C-3), 104.5 (C-5), 160.6 (N-C=N), 161.5 (C-6), 163.7 (C-4), 165.39 (C=O) (Calc. for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.13; H, 7.46; N, 11.03%).

*2-(4-Bromophenyl)-6-methylpyrano[4,3-b]pyrrol-4(1H)-one **4f***. White plates from CH_2Cl_2; mp >300 °C (decomp.); IR (Nujol) ν_{max} 3200 (NH), 1660 (C=O) cm^{-1}; ^{1}H NMR (200 MHz; DMSO-d_6) δ 2.27 (3H, s, Me), 6.5 (1H, s, 7-H), 7.07 (1H, s, 3-H), 7.60–7.80 (4H, m, ArH), 12.25 (1H, br s, NH exchangeable); ^{13}C NMR (50 MHz; DMSO-d_6) δ 19.32 (Me), 95.04 (C-7), 103.00 (C-3), 107.44 (C-3a), 126.23, 131.67 (ArCH), 120.02 and 130.26 (2 × ArC), 133.84 (C-2), 140.72 (C-7a), 155.80 (C-6), 159.38 (C=O) (Calc. for $C_{14}H_{10}BrNO_2$: C, 55.29; H, 3.31; N, 4.61. Found: C, 55.03; H, 3.34; N, 4.55%).

*4-[2-(4-Bromophenyl)-1-morpholinoethylideneamino]-6-methyl-2H-pyran-2-one **5f***. Chestnut plates from EtOH; mp 158 °C; IR (Nujol) ν_{max} 1695 (C=O) cm^{-1}; ^{1}H NMR (200 MHz; $CDCl_3$) δ 2.08 (3H, s, Me), 3.35–3.55 (8H, m, morpholine), 3.69 (2H, s, CH_2), 5.15 (1H, s, 3-H), 5.58 (1H, s, 5-H), 6.94 and 7.37 (4H, dd, AB system, *J* 8.4, ArH) (Calc. for $C_{18}H_{19}BrN_2O_3$: C, 55.38; H, 4.91; N, 7.18. Found: C, 55.17; H, 4.98; N, 6.93%).

*2-(4-Fluorophenyl)-6-methylpyrano[4,3-b]pyrrol-4(1H)-one **4g***. White plates from CH_2Cl_2; mp 248 °C; IR (Nujol) ν_{max} 3100 (NH), 1680 (C=O) cm^{-1}; ^{1}H NMR (200 MHz; DMSO-d_6) δ 2.27 (3H, s, Me), 6.49 (1H, s, 7-H), 7.00 (1H, s, 3-H), 7.20–7.40 and 7.85–7.95 (4H, 2m, ArH), 12.18 (1H, br s, NH exchangeable); ^{13}C NMR (50 MHz; DMSO-d_6) δ 19.31 (Me), 95.04 (C-7), 102.25 (C-3), 107.35 (C-3a), 115.54 and 115.97 (ArCH *ortho* to F, *J* 21.6), 126.33 and 126.48 (ArCH *meta* to F, *J* 7.6), 127.70 (ArC), 134.11 (C-2), 140.46 (C-7a), 155.62 (C-6), 158.9 and 159.46 (CF, *J* 245.0), 159.46 (C=O) (Calc. for $C_{14}H_{10}FNO_2$: C, 69.12; H, 4.15; N, 5.76. Found: C, 68.97; H, 4.05; N, 5.64%).

*4-[2-(4-Fluorophenyl)-1-morpholinoethylideneamino]-6-methyl-2H-pyran-2-one **5g***. White needles from Pr^iOH; mp 126 °C; IR (Nujol) ν_{max} 1690 (C=O) cm^{-1}; ^{1}H NMR (200 MHz; $CDCl_3$) δ 2.13 (3H, s, CH_3), 3.40–3.58 (8H, m, morpholine), 3.75 (2H, s, CH_2), 5.22 (1H, s, 3-H), 5.63 (1H, s, 5-H), 6.95–7.15 (4H, m, ArH) (Calc. for $C_{18}H_{19}FN_2O_3$: C, 65.43; H, 5.80; N, 8.48. Found: C, 65.29; H, 5.87; N, 8.33%).

Method B

A solution of a dihydrotriazole **3a**–**g** (10 mmol) in propan-1-ol (60 ml) was boiled under reflux, progress of the reaction being followed by TLC. After disappearance of the starting material the solvent was removed *in vacuo*, a small amount of residue was dissolved in DMSO-d_6 and the ratio of **4** and **5** was determined by ^{1}H NMR analysis (see Table 1). Compounds **4** and **5** were isolated after column chromatography (cyclohexane–ethyl acetate 3 : 7). The dihydrotriazole **3e** yielded only the amidine **5e**, which was crystallized. Analytical data were in agreement with those previously reported. The reaction times and isolated yields of compounds are collected in Table 2.

Method C. Effect of $BF_3\cdot Et_2O$ with respect to pyrolysis of dihydrotriazoles 3a–e

$BF_3\cdot Et_2O$ (1.9 ml, 15 mmol) in dry toluene (30 ml) was added to a stirred solution of a dihydrotriazole **3a**–**e** (4.2 g, 15 mmol) in dry toluene (25 ml) at rt. The resulting mixture was refluxed for the same time used in the toluene thermal decomposition, after which the reaction was quenched with 10 ml of saturated aq. $NaHCO_3$ (10 ml). The organic phase was separated, and the aqueous phase was extracted with ethyl acetate (4 × 50 ml). The combined organic phases were washed with brine and dried (Na_2SO_4), filtered, and evaporated to dryness. Ratio of **4** and **5** determined by ^{1}H NMR analysis (DMSO-d_6) (see Table 1) of the residue. The crude mixtures containing **4a**–**g** and **5a**–**g** were chromatographed (cyclohexane–ethyl acetate 2 : 8) to afford first the pyrano[4,3-*b*]pyrrol-4-ones **4** and then the amidines **5**. For analytical data of the products previously obtained see above. The reaction times and isolated yields of compounds are collected in Table 2.

2,6-Dimethylpyrano[4,3-*b*]pyrrol-4(1*H*)-one 4e. White needles from Pr^i_2O; mp 157 °C; IR (Nujol) ν_{max} 3090 (NH), 1670 (C=O) cm^{-1}; ^{1}H NMR (200 MHz; $CDCl_3$) δ 2.26 (3H, s, 6-Me), 2.34 (3H, s, 2-Me), 6.27 (1H, s, 7-H), 6.33 (1H, s, 3H), 9.20 (1H, br s, NH exchangeable); ^{13}C NMR (50 MHz; $CDCl_3$) δ 13.5 (2-Me), 20.2 (6-Me), 96.3 (C-7), 103.4 (C-3), 107.8 (C-3a), 133.1 (C-2), 140.64 (C-7a), 155.2 (C-6), 162.4 (C=O) (Calc. for $C_9H_9NO_2$: C, 66.25; H, 5.56; N; 8.58. Found: C, 66.06; H, 5.74; N; 8.73%).

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