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TRANSFORMATION OF *N*-(5-ACETYL-6-METHYL-2-OXO-2*H*-PYRAN-3-YL)BENZAMIDE WITH HYDRAZINES IN THE PRESENCE OF AN ACIDIC CATALYST[#]

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Abstract – 2*H*-Pyran-2-one derivative (**1**) was transformed with heterocyclic hydrazines and 2,4-dinitrophenylhydrazine, under the influence of various acidic catalysts, into *N*-[5-(1-hydrazonoethyl)-6-methyl-2-oxo-2*H*-pyran-3-yl]benzamides (**3**) as the main products, accompanied in some cases by the corresponding (*E*)-α,β-didehydro-α-amino acid derivatives (**4**).

2*H*-Pyran-2-ones and fused pyran-2-ones are important biologically active compounds and synthetic intermediates.[1] They react with nitrogen-containing nucleophiles either at a side chain or by an opening of the pyran-2-one ring and a subsequent ring closure to give various pyridin-2(1*H*)-ones, pyrazoles or other rings.[1b,c,2] Recently, we described a transformation of *N*-(5-acetyl-6-methyl-2-oxo-2*H*-pyran-3-yl)-benzamide (**1**) with various hydrazines into the pyrazoles containing α,β-didehydro-α-amino acid moiety.[3] The reaction took place either as a two-step process *via* the corresponding hydrazone derivative, which was obtained under acidic conditions and further transformed under aqueous basic conditions,[3a] or as a one-pot process under different basic conditions.[3b] More complex reaction was observed in the case of related *N*-(5-benzoyl-6-methyl-2-oxo-2*H*-pyran-3-yl)benzamide, whose reaction with various hydrazines or hydroxylamine in the appropriate solvent (predominantly a mixture of ethanol and pyridine) gave α,β-didehydroamino acid derivatives containing either a pyrazolyl or an isoxazolyl residue at the β-position.[3b,4] With phenylhydrazines possessing electron-withdrawing or sterically bulky groups, as well as with heterocyclic hydrazines, complex (*E/Z*)-mixtures of α,β-didehydroamino acid derivatives and their decarboxylated analogs were usually obtained.

In the related 2*H*-1-benzopyran-2-one series, benzopyran-2,5-diones were selectively converted into

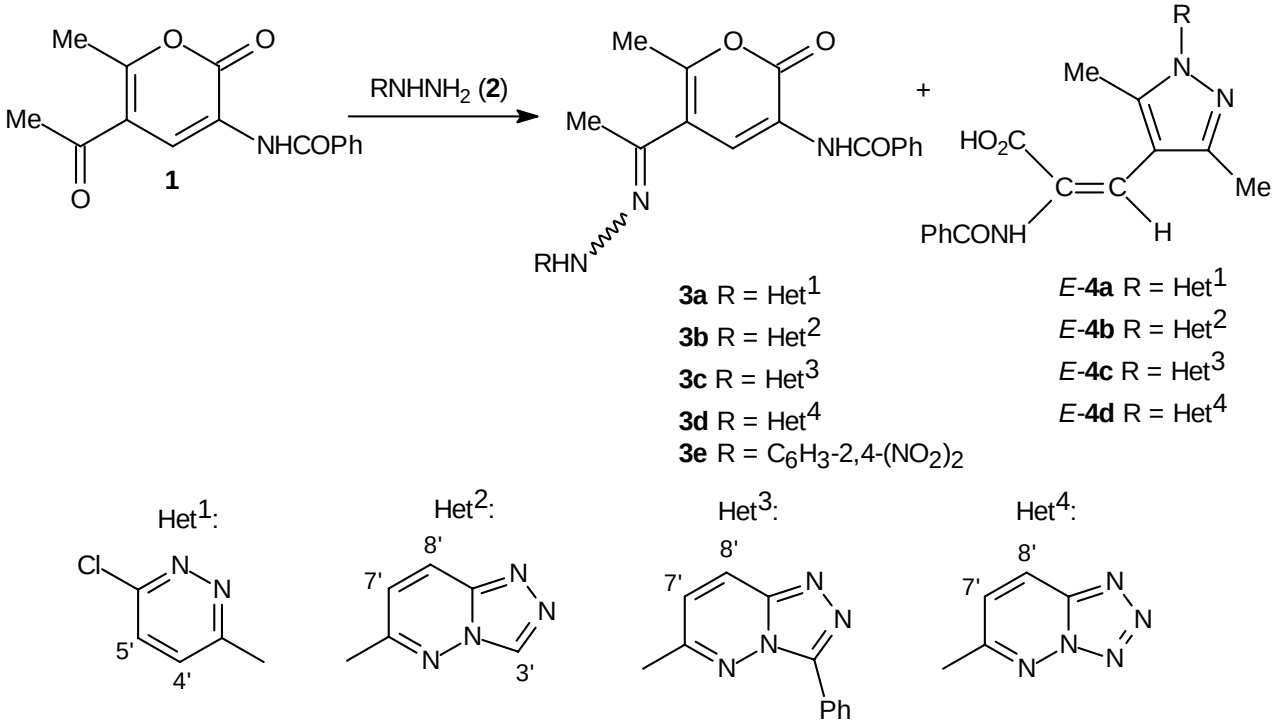
[#] This paper is a small contribution on the occasion of the 30th anniversary of HETEROCYCLES.

5-hydrazonobenzopyrans on treatment with hydrazides, arylhydrazines and heterocyclic hydrazines.[3a,5a–f] These reactions were carried out in dry ethanol under the influence of acidic catalysts or under microwave irradiation in the absence of a solvent. The hydrazones were selectively transformed to the corresponding quinoline-2,5-diones *via* an open-ring intermediate when treated with a mixture of ethanol, water and triethylamine.[3a] In contrast, 5,6,7,8-tetrahydro-2*H*-1-benzopyran-2,8-dione system gave in all the investigated transformations the corresponding 8-hydrazono (or 8-hydroxyimino) derivatives.[5g] In the reactions between 5,6,7,8-tetrahydro-2*H*-1-benzopyran-2,5-diones and various hydrazine derivatives (acetylhydrazine, arylhydrazines and heterocyclic hydrazines) as nitrogen-containing nucleophiles, under alkaline reaction conditions (a mixture of ethanol, water and triethylamine), the corresponding quinoline derivatives were isolated in high yields.[6] The reaction intermediate we isolated allowed a determination of the reaction pathway in which ring opening occurred in the first step followed by the formation of the hydrazone and finally cyclization into the quinoline derivative. Having in mind a straightforward reaction of 2*H*-pyran-2-one (**1**) with a heterocyclic hydrazine into (*E*)-*N*-(5-{1-[(imidazo[1,2-*b*]pyridazin-6-yl)-hydrazono]ethyl}-6-methyl-2-oxo-2*H*-pyran-3-yl)benzamide in dry ethanol and in the presence of an acidic catalyst,[3a] and different reaction courses under acidic and alkaline conditions in the benzopyran-2-one series, we wanted to explore the reaction of the compound (**1**) with various hydrazines towards the corresponding hydrazones under acidic condition by changing solvents, catalysts and temperature.

Herein, we report transformations of 2*H*-pyran-2-one (**1**) with selected heterocyclic hydrazines and 2,4-dinitrophenylhydrazine into 5-hydrazonoethyl-2*H*-pyran-2-one derivatives (**3**) and α,β-didehydro-α-amino acid derivatives (**4**). The results obtained are given in Sheme 1 and Table 1. Reactions were performed predominantly in dry 1,4-dioxane under the influence of *p*-toluenesulfonic acid (TsOH), which gave higher yields of hydrazones (**3**) than previously used mixtures of ethanol/TsOH or ethanol/$BF_3\times Et_2O$ (Runs 1, 5 and 8). An exception was a transformation of the starting compound (**1**) with 3-chloro-6-hydrazinopyridazine where a mixture of products (**3a**) and (***E*-4a**) was obtained in all the cases. Nevertheless, the highest yield of the product (**3a**) was obtained in the mixture of 1,4-dioxane, ether and $BF_3\times Et_2O$ (Run 2). Compounds of type (**4**) were prepared in high yields by a transformation of 2*H*-pyran-2-one (**1**) with hydrazines under basic conditions as previously published.[3b] A treatment of **1** with 2,4-dinitrophenylhydrazine resulted in a complex mixture of products from which only **3e** was isolated in a moderate yield; no better reaction conditions were found for the preparation of the product (**3e**).

Comparing the above results, we can conclude that the products of type (**3**) result from nucleophilic attack (a) at the exocyclic acetyl carbonyl group at the position 5 of the 2*H*-pyran-2-one ring (Scheme 2). A formation of the products of type (**4**) could be explained by the following reaction pathways. The first one involves an intermediate (**5**) and/or the hydrazone intermediate (**3**), which are further transformed into the

compound (**4**).



Scheme 1

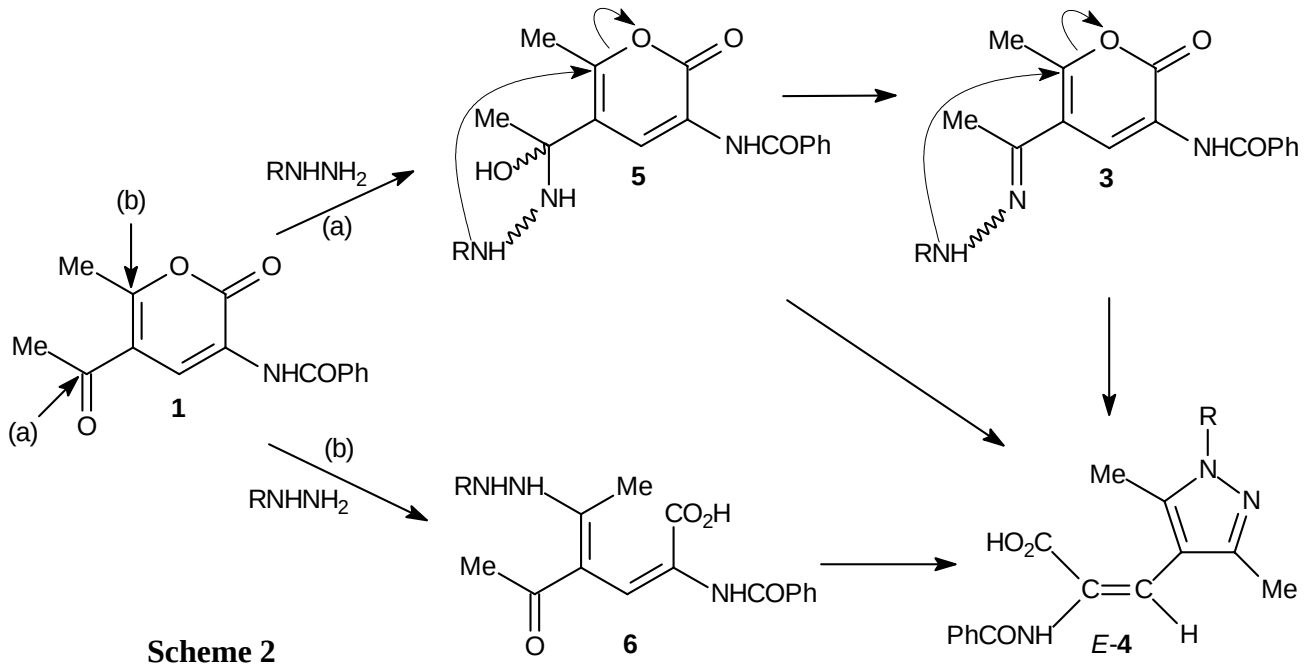
Table 1. Reaction conditions and yields of products (**3**) and (**4**):

Run	SM	Reagent **2** (R=)	Conditions	Products	Yield (%)[a]
1	**1**	Het[1]	A, 90 min, Δ	**3a**/*E*-**4a**: 23/77[b]	70
2	**1**	Het[1]	B, 5 h, rt	**3a**/*E*-**4a**: 50/50[b]	66
3	**1**	Het[1]	C, 30 min, Δ	**1**/**3a**/*E*-**4a**: 25/25/50[b]	59
4	**1**	Het[2]	C, 40 min, Δ	**3b**	88
5	**1**	Het[2]	D, 7 h, Δ	**3b**/*E*-**4b**: 45/55[b]	82
6	**1**	Het[3]	C, 170 min, Δ	**3c**/*E*-**4c**: 75/25[b]	92
7	**1**	Het[4]	C, 110 min, Δ	**3d**	90
8	**1**	Het[4]	A, 120 min, Δ	**3d**/*E*-**4d**: 75/25[b]	93
9	**1**	C_6H_3-2,4-$(NO_2)_2$	C, 150 min, Δ	**3e**	43

A: EtOH/TsOH; B: 1,4-dioxane/ether/$BF_3\times Et_2O$; C: 1,4-dioxane/TsOH; D: EtOH/$BF_3\times Et_2O$. [a]Yields of the isolated products are given. [b]A molar ratio **3**/**4** (and **1**/**3**/**4** in Run 3) was determined on the basis of a ^{1}H NMR spectrum of the crude mixture of products.

An alternative possibility is a nucleophilic attack of the hydrazine molecule at the position 6 of a

2*H*-pyran-2-one derivative [attack (b)] followed by the ring opening to give the intermediate (**6**),[4,7] which cyclizes into the final product ((*E*)-**4**). Since we did not isolate any (*Z*)-**4** derivative, the reaction *via* an open ring intermediate (**6**) seems to be less possible. Two additional types of experiments have shown the complexity of this conversion towards products (**3**). Namely, several attempts to transform the compounds (**3a**, **3b**, **3d** and **3e**) to the products of type (**4**) under basic conditions (EtOH/pyridine), which were used previously[3b] for the synthesis of products of type (**4**) from **1** and the corresponding hydrazine, resulted in the recovery of starting compounds (**3**). Moreover, the compound (**3d**) remained unchanged after heating for a couple of hours under acidic conditions given in Run 8. This probably means that **4d** (in Run 8) was formed either directly *via* intermediate (**5**) (and not forming **3**) or via **6**. Alternatively, a low solubility of hydrazones might also be an explanation of their stability. A transformation of 2*H*-pyran-2-one (**1**) with some other hydrazines (hydrazine hydrate, methyhydrazine, phenylhydrazine), under various reaction conditions, gave only the products of type (**4**). On the basis of all the results obtained one can conclude that due to a strong stereoelectronic effect in 2,4-dinitrophenylhydrazine or heterocyclic hydrazines by the assistance of an acidic catalyst and an appropriate solvent, the attack (a) at the exocyclic carbonyl group at the position 5 in 2*H*-pyran-2-one system was favorable and products of type (**3**) were formed.



Scheme 2

A differentiation between structures of types (**3**) and (**4**) was performed on the basis of their NMR spectral data. Chemical shifts for 4-H of the compounds (**3**) are in the range 8.16–8.26 ppm, while chemical shifts of compounds (**4**) for 3-H can be found in the range of 6.63–6.66 ppm that is typical for (*E*)-**4** derivatives.[3,4]

The signals for the =NN*H* of the hydrazono groups of products (**3**) were found in the range of 9.63–9.68 ppm, which is in agreement with our previous result.[3a] A study of the previously mentioned (*E*)-*N*-(5-{1-[(imidazo[1,2-*b*]pyridazin-6-yl)hydrazono]ethyl}-6-methyl-2-oxo-2*H*-pyran-3-yl)benzamide by 2D NMR spectral technique revealed (*E*)-configuration of the hydrazone C=N double bond.[3a]

In conclusion, we have shown a scope and limitation of the methodology for the synthesis of *N*-[5-(1-hydrazonoethyl)-6-methyl-2-oxo-2*H*-pyran-3-yl]benzamides. The formation of a 5-membered pyrazole derivatives (**4**) from 2*H*-pyran-2-one (**1**) represents an example of the *pseudo ring transformation*,[8] where two atoms from the six-membered pyran-2-one ring are involved in the five-membered pyrazole ring.

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage, and are uncorrected. ^{1}H and ^{13}C NMR spectra, reported in ppm, were obtained on a Bruker Avance DPX 300 spectrometer in DMSO-d_6, using TMS as an internal standard. ^{13}C spectra were referred on a chemical shift of DMSO-d_6 (39.5 ppm). IR spectra, reported in cm^{-1}, were recorded with a Perkin Elmer 1310 or Bio-Rad FTS (Excalibur Series) spectrophotometers. MS spectra, reported in units of *m/z*, were measured with a VG-Analytical AutospecQ instrument. Elemental analyses were performed with a Perkin Elmer 2400 CHN Analyzer. TLC analysis: FLUKA silica gel plates (F_{254}). 2*H*-Pyran-2-one derivative (**1**),[9] 3-chloro-6-hydrazinopyridazine,[10a] 6-hydrazino-1,2,4-triazolo[4,3-*b*]pyridazine,[10b] 6-hydrazino-3-phenyl-1,2,4-triazolo[4,3-*b*]pyridazine,[10c] and 6-hydrazinotetrazolo[1,5-*b*]pyridazine[10b] were prepared as described in the literature. 1,4-Dioxane was dried and distilled prior to use. All other solvents and reagents were used as received from commercial sources.

General procedure. To a mixture of the pyran-2-one derivative (**1**) (1 mmol) and a substituted hydrazine (**2**) (1.1 mmol) was added a mixture of a solvent (5 mL) and a catalyst (0.01 mmol) [For Run 2: 1,4-dioxane (3 mL), ether (3 mL) and $BF_3 \times Et_2O$ (three drops)]. The resulting reaction mixture was stirred at rt or heated under reflux. Upon cooling the products were collected by filtration and washed with a small amount of ethanol [For Run 2: the reaction mixture was first evaporated, then ethanol (10 mL) was added and, upon cooling, the products were filtered off]. Reaction conditions and yields are given in Table 1. All crude mixtures of products were analyzed by ^{1}H NMR technique; all the spectra of compounds ((*E*)-**4a**–**c**) in the mixtures were identical with those described previously.[3b] All the hydrazones were isolated by crystallization from the reaction mixtures. Products of type (**4**) were isolated by a method where the solvent after crystallization was evaporated and water was added to the residue, followed by a basification with 1M

NaOH to pH 9, filtration and acidification of the filtrate with HCl (1:1) to pH 1. The separated product was filtered off and crystallized.

N*-(5-{1-[(6-Chloropyridazin-3-yl)hydrazono]ethyl}-6-methyl-2-oxo-2*H*-pyran-3-yl)benzamide (3a).** The product was obtained after crystallization of the crude mixture of products (**3a**) and (E*-4a**) from DMF/EtOH; mp 184–186 °C; ^{1}H NMR δ 2.28 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 7.59 (m, 5H, Ph, 4'-H and 5'-H), 7.94 (m, 2H, Ph), 8.17 (s, 1H, 4-H), 9.63 (s, 1H, NH), 10.67 (s, 1H, NH); ^{13}C NMR δ 16.9 (CH_3), 18.6 (CH_3), 116.1, 116.8, 122.0, 127.6, 128.5, 130.0, 130.8, 132.1, 133.5, 144.4, 147.9, 155.5, 158.4, 159.4, 165.8; IR (KBr) ν_{max} 1715, 1675, 1640, 1585 cm^{-1}; EIMS (*m/z*) 397 (M^+, 2%), 105 (100%). Anal. Calcd for $C_{19}H_{16}N_5O_3Cl$: C, 57.36; H, 4.05; N, 17.60. Found C, 57.40; H, 4.01; N, 17.58.

N*-(6-Methyl-2-oxo-5-{1-[(1,2,4-triazolo[4,3-*b*]pyridazin-6-yl)hydrazono]ethyl}-2*H*-pyran-3-yl)-benzamide (3b).** In the case of Run 5 this product was obtained after crystallization of the crude mixture of products (**3b**) and (E*-4b**) from DMF/EtOH; mp 227–229 °C; ^{1}H NMR δ 2.28 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 7.41 (d, 1H, J = 10.0 Hz, 7'-H), 7.54 (m, 2H, Ph), 7.62 (m, 1H, Ph), 7.95 (m, 2H, Ph), 8.16 (s, 1H, 4-H), 8.17 (dd, 1H, J_1 = 0.8 Hz, J_2 = 10.0 Hz, 8'-H), 9.28 (d, 1H, J = 0.8 Hz, 3'-H), 9.65 (s, 1H, NH), 10.43 (s, 1H, NH); ^{13}C NMR δ 17.0 (CH_3), 18.5 (CH_3), 114.7, 116.7, 122.0, 124.8, 127.6, 128.5, 130.7, 132.1, 133.4, 138.4, 142.5, 145.4, 153.5, 155.6, 158.4, 165.8; IR (KBr) ν_{max} 1707, 1665, 1647, 1619, 1600 cm^{-1}; EIMS (*m/z*) 403 (M^+, 5%), 105 (100%). Anal. Calcd for $C_{20}H_{17}N_7O_3$: C, 59.55; H, 4.25; N, 24.31. Found C, 59.33; H, 4.46; N, 24.26.

N*-(6-Methyl-2-oxo-5-{1-[(3-phenyl-1,2,4-triazolo[4,3-*b*]pyridazin-6-yl)hydrazono]ethyl}-2*H*-pyran-3-yl)benzamide (3c).** The product was obtained after crystallization of the crude mixture of products (**3c**) and (E*-4c**) from DMF/EtOH; mp 242–245 °C; ^{1}H NMR δ 2.32 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 7.43 (d, 1H, J = 10.2 Hz, 7'-H), 7.46 (m, 1H, Ph), 7.55 (m, 4H, Ph), 7.63 (m, 1H, Ph), 7.97 (m, 2H, Ph), 8.23 (d, 1H, J = 10.2 Hz, 8'-H), 8.26 (s, 1H, 4-H), 8.52 (m, 2H, Ph), 9.67 (s 1H, NH), 10.44 (s, 1H, NH); ^{13}C NMR δ 17.0 (CH_3), 18.8 (CH_3), 114.2, 116.5, 122.0, 125.2, 126.7, 126.8, 127.6, 128.5, 128.6, 129.5, 130.9, 132.1, 133.5, 144.1, 145.6, 146.1, 153.1, 156.0, 158.4, 165.8; IR (KBr) ν_{max} 1705, 1663, 1618 cm^{-1}; MS (*m/z*) 480 (MH^+). Anal. Calcd for $C_{26}H_{21}N_7O_3$: C, 65.13; H, 4.41; N, 20.45. Found C, 64.88; H, 4.72; N, 20.50.

N*-(6-Methyl-2-oxo-5-{1-[(tetrazolo[1,5-*b*]pyridazin-6-yl)hydrazono]ethyl}-2*H*-pyran-3-yl)-benzamide (3d).** In the case of Run 8 this product was obtained after crystallization of the crude mixture of products (**3d**) and (E*-4d**) from DMF/EtOH; mp 255–258 °C; ^{1}H NMR δ 2.32 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 7.54 (m, 2H, Ph), 7.63 (m, 1H, Ph), 7.77 (d, 1H, J = 9.8 Hz, 7'-H), 7.95 (m, 2H, Ph), 8.20 (s, 1H, 4-H), 8.50 (d, 1H, J = 9.8 Hz, 8'-H), 9.66 (s, 1H, NH), 10.94 (s, 1H, NH); ^{13}C NMR δ 17.2 (CH_3), 18.6 (CH_3), 116.5, 118.2, 122.0, 124.8, 127.6, 128.5, 130.6, 132.1, 133.4, 140.9, 147.1, 155.1, 155.9, 158.3, 165.8; IR

(KBr) ν_{max} 1720, 1672, 1625 cm^{-1}; EIMS (*m/z*) 404 (M^+, 3%), 105 (100%). Anal. Calcd for $C_{19}H_{16}N_8O_3$: C, 56.43; H, 3.99; N, 27.71. Found C, 56.59; H, 4.09; N, 27.71.

***N*-(5-{1-[(2,4-Dinitrophenyl)hydrazono]ethyl}-6-methyl-2-oxo-2*H*-pyran-3-yl)benzamide (3e):** mp 237-240 °C (EtOH/DMF); ^{1}H NMR δ 2.41 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 7.54 (m, 2H, Ph), 7.62 (m, 1H, Ph), 7.94 (m, 3H, Ph), 8.24 (s, 1H, 4-H), 8.43 (dd, 1H, J_1 = 2.6 Hz, J_2 = 9.6 Hz, Ph), 8.91 (d, 1H, J = 2.6 Hz, Ph), 9.68 (s, 1H, NH), 11.01 (s, 1H, NH); ^{13}C NMR δ 16.6 (CH_3), 18.8 (CH_3), 116.07, 116.14, 122.2, 123.0, 127.6, 128.5, 129.9, 130.0, 130.3, 132.1, 133.4, 151.2, 156.6, 158.2, 165.8 (two signals hidden); IR (KBr) ν_{max} 1717, 1680, 1625, 1600 (br) cm^{-1}; EIMS (*m/z*) 451 (M^+, 7%), 105 (100%). Anal. Calcd for $C_{21}H_{17}N_5O_7$: C, 55.88; H, 3.80; N, 15.51. Found C, 55.83; H, 3.61; N, 15.73.

(*E*)-2-(Benzoylamino)-3-[1-(6-chloro-3-pyridazin-6-yl)-3,5-dimethyl-1*H*-pyrazol-4-yl]propenoic acid (*E*-4d): mp 187–189 °C (EtOH/DMF) (lit.,[3b] mp 187–189 °C).

(*E*)-2-(Benzoylamino)-3-[3,5-dimethyl-1-(1,2,4-triazolo[4,3-*b*]pyridazin-6-yl)-1*H*-pyrazol-4-yl]-propenoic acid (*E*-4b): mp 253–255 °C (EtOH/DMF) (lit.,[3b] mp 253–255 °C).

(*E*)-2-(Benzoylamino)-3-[3,5-dimethyl-1-(3-phenyl-1,2,4-triazolo[4,3-*b*]pyridazin-6-yl)-1*H*-pyrazol-4-yl]propenoic acid (*E*-4c): mp 285–288 °C (EtOH/DMF) (lit.,[3b] mp 285–288 °C).

(*E*)-2-(Benzoylamino)-3-[3,5-dimethyl-1-(tetrazolo[1,5-*b*]pyridazin-6-yl)-1*H*-pyrazol-4-yl]propenoic acid (*E*-4d): mp 246–248 °C (EtOH/DMF) (lit.,[3b] mp 246–248 °C).

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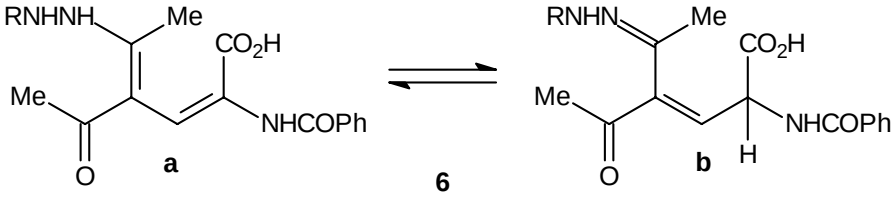
7. Two tautomeric forms (**a** and **b**) of the intermediate (**6**) have been postulated for the formation of α,β-didehydro-α-amino acid derivatives (**4**).[4] The intermediate (**6**) can be transformed into products ((*E*)-**4**) *via* the tautomeric form (**6a**) or eventually *via* **6b** (probably in addition to *Z*-**4**), but *Z*-**4** can only be formed *via* intermediate (**6b**), which possesses a single bond between C-2 and C-3.



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