Chemistry of Heterocyclic Compounds, Vol. 44, No. 7, 2008

UNUSUAL REACTION OF 5-BENZOYL-3-ETHOXYCARBONYL-6-METHYLTHIO-1-R-1,2-DIHYDROPYRIDIN-2-ONES WITH NITROGEN-CONTAINING 1,4-DINUCLEOPHILES

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The reaction of 5-benzoyl-3-ethoxycarbonyl-6-methylthio-1-R-1,2-dihydropyridin-2-ones with the nitrogen-containing 1,4-dinucleophiles o-phenylenediamine, o-aminothiophenol, and ethylenediamine, proceeds as a recyclization, the products of which are derivatives of 5-(1H-benzimidazol-2-yl)-2H-2-pyranone, 5-(benzothiazol-2-yl)-2H-2-pyranone, and 5-(4,5-dihydro-1H-imidazol-2-yl)-2H-2-pyranone respectively.

Keywords: *o*-aminothiophenol, 5-(1H-benzimidazol-2-yl)-3-benzoyl-6-(R-amino)-2H-2-pyranones, 5-(benzothiazol-2-yl)-3-benzoyl-6-(R-amino)-2H-2-pyranones, 5-benzoyl-3-ethoxycarbonyl-6-methylthio-1-R-1,2-dihydropyridin-2-ones, *o*-phenylenediamine, ethylenediamine, X-ray structural analysis, recyclization.

Methods are given in [1-5] for the synthesis of 5-aroyl-6-methylthio-3-R-1,2-dihydropyridin-2-ones, which are polyfunctional compounds and valuable substrates for transformation into condensed bi- or tricyclic nitrogen-containing heterosystems. However further heterocyclizations of these reactants were not completely studied, probably because of the absence of satisfactory methods of obtaining them.

Recently we developed a preparative method for the selective synthesis of 5-benzoyl-3-ethoxycarbonyl-6-methylthio-1-R-1,2-dihydropyridin-2-ones **1a,b** from accessible starting materials, and have shown that they may be used as synthesis blocks for cyclocondensations with nitrogen-containing 1,2- and 1,3-dinucleophiles [6].

The aim of the present work was the evaluation of the synthetic potential of 5-benzoyl-3-ethoxycarbonyl-6-methylthio-1-R-1,2-dihydropyridin-2-ones **1a,b** in reactions with the nitrogen-containing 1,4-dinucleophiles *o*-phenylenediamine **2a**, *o*-aminothiophenol **2b**, and ethylenediamine **6**. It was assumed that the interaction of dihydropyridin-2-ones **1a,b** with reactants **2a,b** must occur at the methylthio and benzoyl groups of substrates **1a,b** with the formation of 3-ethoxycarbonyl-5-phenyl-1-R-2,6-dihydro-1H-benzo[*b*]pyrido[2,3-*e*]-[1,4]diazepin-2-ones **3a,b** and 3-ethoxycarbonyl-5-phenyl-1-R-1,2-dihydrobenzo[*b*]pyrido[2,3-*e*][1,4]thiazepin-2-ones **3c,d**.

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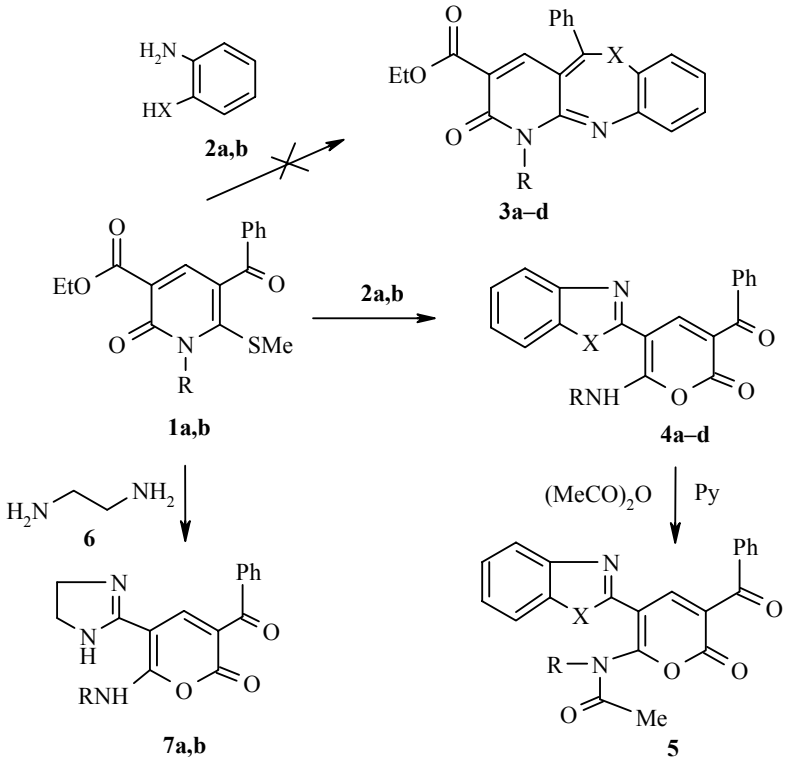
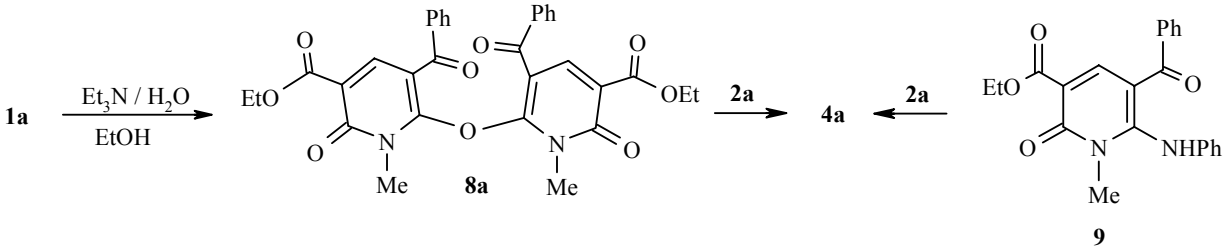
However it was established that the reaction of 1,2-dihydropyridin-2-ones **1a,b** with reactants **2a,b** was accomplished by a different scheme. The products of this condensation proved to be not the expected diazepines (or thiazepines) **3a-d**, but 5-(1H-benzimidazol-2-yl)-3-benzoyl-6-(R-amino)-2H-2-pyranones **4a,b** and 5-(benzothiazol-2-yl)-3-benzoyl-2-yl)-6-(R-amino)-2H-2-pyranones **4c,d**, which are the result of a recyclization process.



1a, **3a**,**c**, **4a**,**c**, **5**, **7a** R = Me; **1b**, **3b**,**d**, **4b**,**d**, **7b** R = Et;
2a, **3a**,**b**, **4a**,**b**, **5** X = NH; **2b**, **3c**,**d**, **4c**,**d** X = S

Dihydropyridin-2-ones **1a,b** also react with 1,2-ethylenediamine **6** in a similar way. 3-Benzoyl-5-(4,5-dihydro-1H-imidazol-2-yl)-(6-R-amino)-2H-2-pyranones **7a,b** were isolated from the reaction mixture (Table 1).

The structure of 2H-2-pyranones **4a-d, 7a,b** was demonstrated with the aid of ^{1}H and ^{13}C NMR spectroscopy and IR spectroscopy (Table 2), and also by conversion of compound **4a** into 6-(N-acetyl-N-methylamino)-5-(1H-benzimidazol-2-yl)-3-benzoyl-2H-2-pyranone (**5**) by the action of acetic anhydride in pyridine.



We carried out two model reactions to clarify the mechanism of formation of 2H-2-pyranone derivatives **4a-d** and **7a,b**. It was established that elimination of the methylthio group of 1,2-dihydropyrin-2-one **1a** was also effected by the action of aqueous alcoholic triethylamine solution, when the hydrolysis product was 1,2-dihydropyridine **8a**. The latter reacts readily with *o*-phenylenediamine **2a** with the formation of 2H-2-pyranone **4a**

TABLE 1. Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %				mp, °C*	Yield, %
		C	H	N	S		
4a	$C_{20}H_{15}N_3O_3$	69.74 / 69.56	4.31 / 4.38	12.13 / 12.17		283-285	70
4b	$C_{21}H_{17}N_3O_3$	69.89 / 70.18	4.56 / 4.77	11.85 / 11.69		272-275	63
4c	$C_{20}H_{14}N_2O_3S$	66.02 / 66.29	4.15 / 3.89	7.48 / 7.73	8.64 / 8.85	250-252	61
4d	$C_{21}H_{16}N_2O_3S$	66.73 / 67.01	4.42 / 4.28	7.29 / 7.44	8.40 / 8.25	241-243	57
5	$C_{22}H_{17}N_3O_4$	68.06 / 68.21	4.33 / 4.42	11.09 / 10.85		245-247	75
7a	$C_{16}H_{15}N_3O_3$	64.37 / 64.64	4.98 / 5.09	14.30 / 14.13		335-337	69
7b	$C_{17}H_{17}N_3O_3$	65.60 / 65.58	5.58 / 5.50	13.61 / 13.50		300-303	63
8a	$C_{32}H_{28}N_2O_9$	65.94 / 65.75	4.66 / 4.83	4.64 / 4.79		100-101	52

* Compounds **4a-d, 5, 7a,b** were recrystallized from DMSO, compound **8a** from 2-propanol.

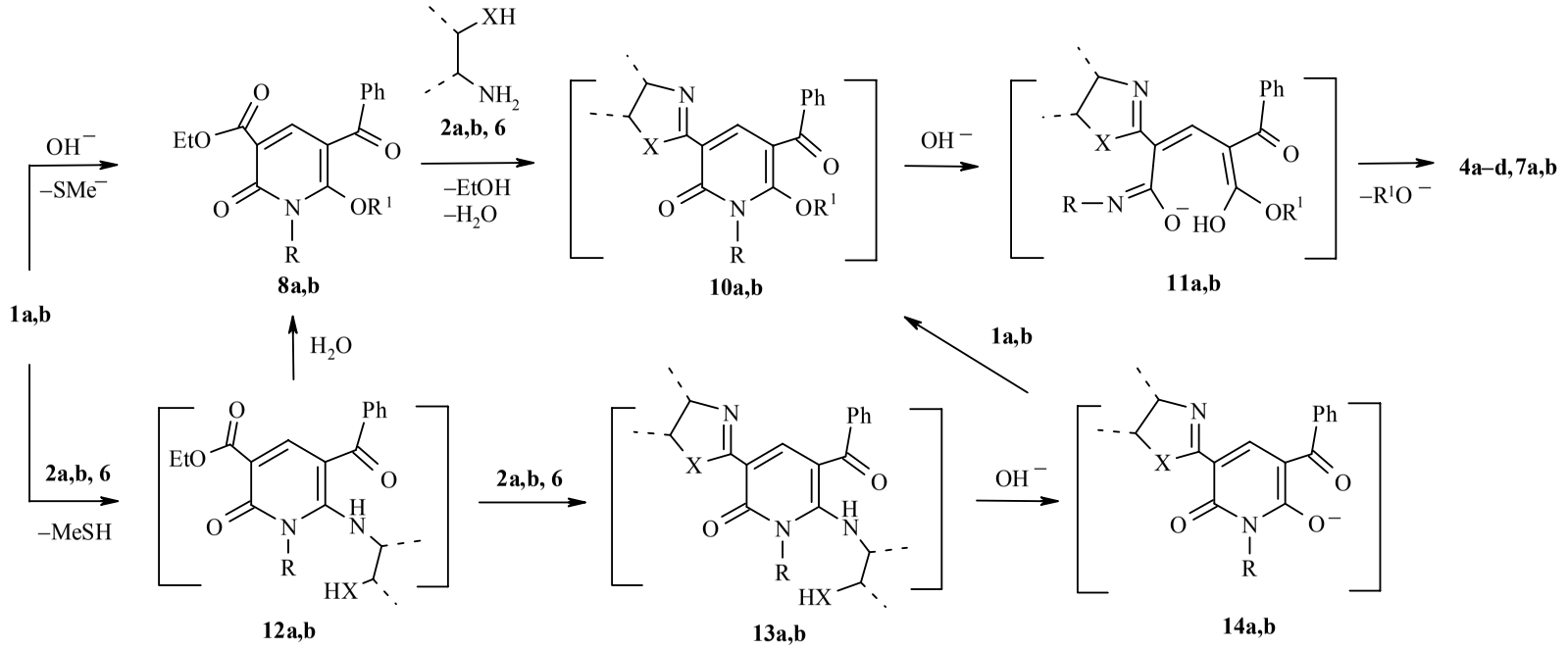
(72% yield). 2H-2-Pyranone **4a** was also synthesized by the reaction of 5-benzoyl-3-ethoxycarbonyl-1-methyl-6-phenylamino-1,2-dihydropyridin-2-one **9** with *o*-phenylenediamine **2a**, but in this way the yield of the desired product did not exceed 39%.

The characteristic signals in the ^{1}H NMR spectra, confirming the formation of products **4a-d**, **5**, and **7a,b**, are doublets for the CH_3NH group (compounds **4a,c**, **7a**, δ 2.75-2.87 ppm, J = 2.7-4.2 Hz) and singlets for the (benz)imidazole NH groups (compounds **4a,b**, **5**, and **7a,b** at 13.71-13.78 and 9.37-9.39 ppm respectively). In the IR spectra of all the 2H-2-pyranones **4a-d**, **5**, and **7a,b** absorption bands were observed for the stretching vibrations of the NH group (3250-3400 cm^{-1}). The presence of a carbonyl group of the aroyl fragment in compounds **4a-d**, **5**, **7a,b**, and **8a** was identified with the aid of ^{13}C NMR spectroscopy, since in the spectra of the initial compounds **1a,b** [6] and products **4a**, **7b**, and **8a** the signals of the Ph-C=O carbon atom are extremely characteristic (191.0-192.6 ppm).

On the basis of the experimental data obtained the following scheme may be suggested for the mechanism of recyclization of dihydropyridin-2-ones **1a,b** into 2H-2-pyranones **4a-d, 7a,b**. Probably the first stages of the reaction are hydrolysis and amination of dihydropyridin-2-ones **1a,b** into the intermediates **8a,b** and **12a,b** respectively.

To all appearances, attack of the 1,4-nucleophile is then effected at the ester group of 1,2-dihydropyridin-2-ones **8a,b** and **12a,b**, as a result of which 3-heteryl-1,2-dihydropyridin-2-ones **10a,b** and **13a,b** are formed. The intermediate **13a,b** may be converted into the intermediate product **14a,b** on attack by hydroxyl ion. The pyridine ring of the intermediate **10a,b** is opened under the action of nucleophile (intermediate product **11a,b**), then intramolecular nucleophilic attack occurs, as a result of which 2H-2-pyranones **4a-d**, **7a,b** are obtained. The reason for the recyclization in fact is the presence of two withdrawing substituents (benzoyl and heteryl [7]) in the pyridine ring of the intermediate compounds **10a,b**, which facilitates the ANRORC process beginning with attack of the nucleophile at position 6 of the pyridine ring. Probably a definite contribution to the ease of carrying out the reaction is also introduced by the high thermodynamic stability of the resulting 2H-2-pyranones **4a-d, 7a,b**.

The 2H-2-pyranone derivatives **4a-d**, **5**, and **7a,b** are high melting substances of a yellow color, poorly soluble in polar organic solvents. It should be mentioned that 2H-2-pyranones containing a 1H-benzimidazole



8, **10–14** **a** R = Me, **b** R = Et; **8a**,**b, 10a**,**b**, **11a**,**b** R^1 = 5-benzoyl-3-ethoxycarbonyl-1-methyl-2-oxo-1-R-1,2-dihydropyridin-6-yl

TABLE 2. Data of IR and ^{1}H NMR Spectroscopy of the Synthesized Compounds

Com-pound	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum, δ, ppm (*J*, Hz)
4a	3330, 3000, 1675, 1620, 1600, 1560, 1540, 1470, 1450, 1390, 1370	2.85 (3H, d, *J* = 3.6, NHC<u>H</u>$_3$); 7.48 (1H, m, H$_{Ar}$); 7.63-7.69 (6H, m, H$_{Ar}$); 7.84 (1H, m, H$_{Ar}$); 8.68 (1H, s, H-4); 8.70 (1H, m, H$_{Ar}$); 9.00 (1H, br. s, N<u>H</u>CH$_3$); 13.71 (1H, s, NH$_{Het}$)
4b	3330, 3000, 1685, 1610, 1560, 1470, 1440, 1390, 1370, 1340, 1320, 1260, 1230	1.16 (3H, t, *J* = 6.3, NHCH$_2$C<u>H</u>$_3$); 3.36 (2H, m, NHC<u>H</u>$_2$CH$_3$); 7.49 (1H, m, H$_{Ar}$); 7.62-7.76 (6H, m, H$_{Ar}$); 7.88 (1H, m, H$_{Ar}$); 8.69 (1H, s, H-4); 8.71 (1H, m, H$_{Ar}$); 9.11 (1H, br. s, N<u>H</u>Et); 13.73 (1H, s, NH$_{Het}$)
4c	3350, 3000, 1670, 1615, 1560, 1490, 1460, 1420, 1380, 1330	2.87 (3H, d, *J* = 2.7, NHC<u>H</u>$_3$); 7.66 (7H, m, H$_{Ar}$); 8.23 (1H, m, H$_{Het}$-7); 8.74 (1H, s, H-4); 9.02 (1H, br. s, N<u>H</u>CH$_3$); 9.20 (1H, m, H$_{Het}$-4)
4d	3300, 3000, 1690, 1620, 1570, 1500, 1470, 1385, 1310, 1250	1.18 (3H, t, *J* = 6.6, NHCH$_2$C<u>H</u>$_3$); 3.34 (2H, m, NHC<u>H</u>$_2$CH$_3$); 7.68-7.83 (7H, m, H$_{Ar}$); 8.26 (1H, m, H$_{Het}$-7); 8.78 (1H, s, H-4); 9.15 (1H, br. s, N<u>H</u>Et); 9.24 (1H, m, H$_{Het}$-4)
5	3250, 3000, 2950, 1690, 1670, 1620, 1560, 1540, 1490, 1460, 1390	2.28 (3H, s, CH$_3$CO); 3.16 (3H, c, NC<u>H</u>$_3$); 7.51 (1H, m, H$_{Ar}$); 7.55-7.72 (6H, m, H$_{Ar}$); 7.87 (1H, m, H$_{Ar}$); 8.18 (1H, s, H-4); 8.70 (1H, m, H$_{Het}$-4); 13.78 (1H, s, NH$_{Het}$)
7a	3380, 3300, 3050, 2970, 1680, 1640, 1600, 1580, 1500	2.75 (3H, d, *J* = 4.2, NHC<u>H</u>$_3$); 3.91 (2H, m, 5'-CH$_2$); 4.14 (2H, t, *J* = 9.3, 4'-CH$_2$); 7.52 (5H, m, C$_6$H$_5$); 8.31 (1H, s, H-4); 8.90 (1H, br. s, N<u>H</u>CH$_3$); 9.39 (1H, br. s, NH$_{Het}$)
7b	3400, 3300, 3100, 3000, 1680, 1640, 1610, 1580, 1500, 1450, 1380, 1330	1.08 (3H, t, *J* = 7.2, NHCH$_2$C<u>H</u>$_3$); 3.21 (2H, m, NHC<u>H</u>$_2$CH$_3$); 3.92 (2H, m, 5'-CH$_2$); 4.13 (2H, t, *J* = 9.0, 4'-CH$_2$); 7.52 (5H, m, C$_6$H$_5$); 8.32 (1H, s, H-4); 9.02 (1H, br. s, N<u>H</u>Et); 9.37 (1H, br. s, NH$_{Het}$)
8a	3100, 3000, 1730, 1680, 1600, 1530, 1460, 1400, 1380, 1310	1.24 (3H, t, *J* = 6.9, OCH$_2$C<u>H</u>$_3$); 3.29 (3H, s, NCH$_3$); 4.19 (2H, q, *J* = 6.9, OC<u>H</u>$_2$CH$_3$); 7.56-7.67 (5H, m, C$_6$H$_5$); 8.18 (1H, s, H-4)

(or benzothiazole, 4,5-dihydro-1H-imidazole) substituent in position 5 of the heterocyclic ring have not been described up to now, which enables us to designate the recyclization investigated by us as new, and as a method of preparative value for the synthesis of previously unknown compounds. In fact the given reaction is a retrorecyclization involving conversion of 2H-2-pyranone into 2-oxo-1,2-dihydropyridines occurring under the action of ammonia and methylamine, respectively, into the methyl ester of coumalic acid [8] and 3,4,6-triphenyl-2H-2-pyranone [9].

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Varian-300 instrument (300 and 75 MHz respectively) in DMSO-d$_6$, internal standard was TMS. The IR spectra were recorded on a UR 20 instrument in KBr disks. 5-Benzoyl-3-ethoxycarbonyl-1-methyl-6-phenylamino-1,2-dihydropyridin-2-one **10** was synthesized by the procedure of [6].

5-(1H-Benzimidazol-2-yl)-3-benzoyl-6-(R-amino)-2H-2-pyranones 4a,b and 5-(Benzothiazol-2-yl)-3-benzoyl-6-(R-amino)-2H-2-pyranones 4c,d. A solution of 5-benzoyl-3-ethoxycarbonyl-6-methylthio-1-R-

1,2-dihydropyridin-2-one **1a,b** (1 mmol) and *o*-phenylenediamine **2a** (or *o*-aminothiophenol **2b**) (1 mmol) in 2-propanol (5 ml) was boiled under reflux for 8 h, cooled, and the solid **4a-d** filtered off.

Compound 4a. ^{13}C NMR spectrum, δ, ppm: 25.7 (NCH_3); 99.4, 105.6, 113.0, 116.4, 123.5, 126.8, 126.9, 128.4, 128.5, 131.2, 131.5, 138.5 (C_{Ar}); 144.1 (C-3); 144.9 (C-6); 159.4 (C-2'); 163.8 (C-2); 191.2 (C_6H_5–C=O).

6-(N-Acetyl-N-methylamino)-5-(1H-benzimidazol-2-yl)-3-benzoyl-2H-2-pyranone (5). A solution of 2H-2-pyranone **4a** (0.345 g, 1 mmol) and pyridine (0.158 g, 2 mmol) in acetic anhydride (1.02 g, 10 mmol) was boiled under reflux for 8 h, cooled, and solid **5** filtered off.

3-Benzoyl-5-(4,5-dihydro-1H-imidazol-2-yl)-6-(R-amino)-2H-2-pyranones 7a,b. A solution of 1,2-dihydropyridin-2-one **1a,b** (1 mmol) and ethylenediamine **6** (0.180 g, 3 mmol) in 2-propanol (5 ml) was boiled under reflux for 2 h, cooled, and solid **7a,b** filtered off.

Compound 7b. ^{13}C NMR spectrum, δ, ppm: 14.8 (NCH_2CH_3); 33.2 (C-5'); 43.1 (NCH_2CH_3); 43.4 (C-4'); 97.7 (C-4); 106.5 (C-5); 127.8, 128.3, 130.7, 138.8 (C_{Ar}); 146.4 (C-3); 156.3 (C-3′); 160.3 (C-6); 162.8 (C-2); 191.3 (C_6H_5–C=O).

5-Benzoyl-6-(5-benzoyl-3-ethoxycarbonyl-1-methyl-2-oxo-1,2-dihydropyrid-6-yl)oxy-3-ethoxycarbonyl-1-methyl-2-oxo-1,2-dihydropyridine (8a). A solution of 1,2-dihydropyridin-2-one **1a** (0.331 g, 1 mmol) and triethylamine (0.303 g, 3 mmol) in 75% ethanol (3 ml) was boiled under reflux for 10 h. The solvent was then evaporated, and the oily residue dissolved in water (3 ml). Acetic acid (several drops) was added, the mixture cooled to 5 °C, and the solid **8a** was filtered off. ^{13}C NMR spectrum, δ, ppm: 14.0 (OCH_2CH_3); 26.6 (NCH_3); 60.3 (OCH_2CH_3); 104.4 (C-4); 105.5 (C-3); 128.5, 128.8, 132.3, 135.2 (C_{Ph}); 144.1 (C-5); 160.3 (C-6); 164.8 (C-2); 166.5 (CO_2Et); 191.0 (C_6H_5–C=O).

Recyclization of 5-Benzoyl-6-(5-benzoyl-3-ethoxycarbonyl-1-methyl-2-oxo-1,2-dihydropyridin-6-yl)-oxy-3-ethoxycarbonyl-1-methyl-2-oxo-1,2-dihydropyridine (8a) and 5-Benzoyl-3-ethoxycarbonyl-1-methyl-6-phenylamino-1,2-dihydropyridin-2-one (9) into 3-Benzoyl-5-(1H-benzimidazol-2-yl)-6-(methyl-amino)-2H-2-pyranone (4a). A solution of 1,2-dihydropyridine **8a** (or **9**) (1 mmol) and *o*-phenylenediamine **2a** (0.216 g or 0.108 g) in 2-propanol (5 ml) was boiled under reflux for 8 h, cooled, and solid compound **4a** filtered off. Yields were 0.497 g (72%) and 0.135 g (39%) respectively. The mp and ^{1}H NMR spectra of compound **4a** obtained by the reaction of pyridin-2-ones **1a**, **8a**, and **9** with *o*-phenylenediamine were identical.

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