Pergamon

Tetrahedron Vol. 51, No. 11, pp. 3279-3288, 1995
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0040-4020/95 $9.50+0.00

0040-4020(95)00050-X

α-Pyrones. Part V.[1] Structure Effects on the Intramolecular Cyclization of Functionalized 6-Pyronylacetamides: Synthesis of New 2,5,7-Trioxo-pyrano [3,2-*c*]pyridines

Francesca Clerici,[a] Maria L. Gelmi,[a]* Barbara Galbiati,[a] Sabrina Mottadelli,[a] Michele Penso,[b] and Donato Pocar[a]

[a]Istituto di Chimica Organica, Facoltà di Farmacia, Università di Milano,Via Venezian 21, I-20133 Milano, Italy.

[b]Centro C.N.R.-C.S.S.S. Speciali Sistemi Organici, Via Golgi 19, I-20133 Milano, Italy.

Abstract: Reaction of arylisocyanates **2** with methyl 2-oxo-2*H*-pyran-6-acetate **1** and with ylide **4** gave two classes of pyronylacetamides **3** and **5**, respectively. Phosphoranes **5** were reduced to the corresponding acetamides **6** with zinc and acetic acid. Compounds **6** were alkylated under solid-liquid PTC conditions using anhydrous potassium carbonate as a base to give the C_α-alkyl derivatives **7** in good yields. Intramolecular cyclization with different bases and solvents of acetamides **3**, **5**-**7** to give the new 2,5,7-trioxo-pyrano[3,2-*c*]pyridines has been studied.

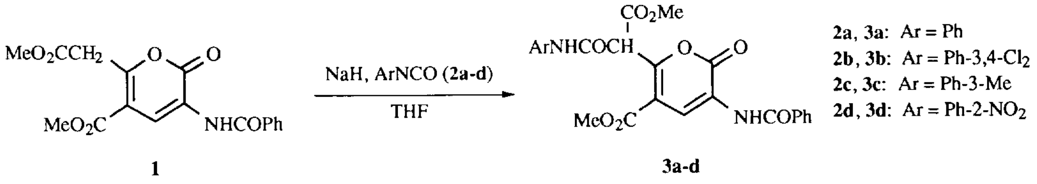
The synthesis of highly functionalized 2*H*-pyrones and of condensed *N*-heterocycles containing the 2*H*-pyrone ring has been the aim of our research for a long time. Both functionalization of the side chains and ring transformations were described in previous papers.[1-4]

In continuation of this project we now report on simple and selective methods for the preparation of highly substituted amides of 5-alkoxycarbonyl-2-oxo-2*H*-pyran-6-acetic acids **5** and of their α-substituted derivatives **3**, **6** and **7** (Schemes 1, 2). Their intramolecular condensation can give substituted 2,5,7-trioxo-pyrano[3,2-*c*]pyridines.[5] The effect of the α-substituents on the acetamido group in the cyclization reaction has been clarified. To our present knowledge this class of compounds has not been disclosed previously. Instead, several syntheses of 2-oxo- and 2,5-dioxo-pyrano[3,2-*c*]pyridines are known.[6-13] As a general rule these heterocycles were obtained starting from a preformed *N*-containing ring, *i.e.* 4-hydroxypyridines or 4-hydroxy-2-pyridones, respectively, by condensation with α,β-unsaturated carbonyl compounds or with reagents with acidic methylenic protons. A single example of another synthetic path leading to a 2,5-dioxo-pyrano[3,2-*c*]pyridine is the reaction of a 2,5-dioxo-pyrano[4,3-*b*]pyran with an amine.[10]

RESULTS AND DISCUSSION

Four classes of amides **3**, **5**-**7** all of which have in common the 3-(benzoylamino)-5-(alkoxycarbonyl)-2-oxo-2*H*-pyran-6-yl group, have been prepared starting from readily available materials. In all cases the amide forming step proceeds through the selective reaction of organic isocyanates with a carbanionic centre generated in the C-6 side-chain of the starting pyrone compound. This synthetic route was chosen as the sole practical synthesis. Typical reactions of amines with esters or acidic chlorides were considered, but proved to be of scarce utility owing to the high reactivity displayed by the pyrone ring toward nucleophilic reagents, mainly *N* containing ones, which promptly react at C-6 (Michael addition) or at the lactone carbonyl group.[14,15] Moreover, the presence of the alkoxycarbonyl group on C-5 increases the selectivity problems.

Malonamides **3a-d** were obtained in satisfactory yields by reacting the readily available[16] 2-oxo-2*H*-pyran-6-acetate **1** with arylisocyanates **2a-d** at room temperature in anhydrous tetrahydrofuran with sodium hydride as a base (Scheme 1).

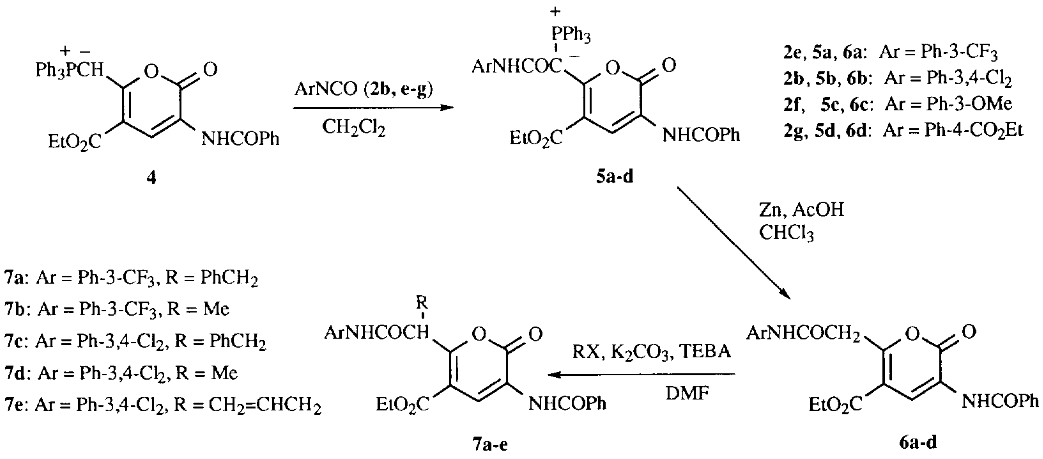


2a, 3a: Ar = Ph
2b, 3b: Ar = Ph-3,4-Cl_2
2c, 3c: Ar = Ph-3-Me
2d, 3d: Ar = Ph-2-NO_2

Scheme 1

The structure of compounds **3** is confirmed by IR (ν_{max} 3250-3400 cm^{-1} NH groups; 1760, 1740, 1720, 1650 cm^{-1} corresponding to lactone, esters and amide groups, respectively) and ^1H NMR spectra where, besides the expected signals for the aryl and methoxycarbonyl groups, four singlets at 9.8-10.8 ppm, 8.6-9.9 ppm (NH, exchangeable with D_2O), 8.5-8.9 ppm (H-4)[2] and 5.5-5.9 (C*H*CO_2Me, exchangeable with D_2O) are present.

Hydrolysis and decarboxylation of malonamides **3** to obtain the simple acetamides **6** were considered. However, only unsatisfactory results were obtained for lack of sitoselectivity of the hydrolysis reaction.



2e, 5a, 6a: Ar = Ph-3-CF_3
2b, 5b, 6b: Ar = Ph-3,4-Cl_2
2f, 5c, 6c: Ar = Ph-3-OMe
2g, 5d, 6d: Ar = Ph-4-CO_2Et

7a: Ar = Ph-3-CF_3, R = $PhCH_2$
7b: Ar = Ph-3-CF_3, R = Me
7c: Ar = Ph-3,4-Cl_2, R = $PhCH_2$
7d: Ar = Ph-3,4-Cl_2, R = Me
7e: Ar = Ph-3,4-Cl_2, R = CH_2=$CHCH_2$

Scheme 2

Instead, a good synthesis which allowed the obtention of compounds **5** together with acetamides **6** was developed by using the readily accessible synthon ethyl 3-(benzoylamino)-2-oxo-6-(triphenylphosphoranylidene)-2*H*-pyran-5-carboxylate **4**.[2] The two-step route is indicated in Scheme 2.

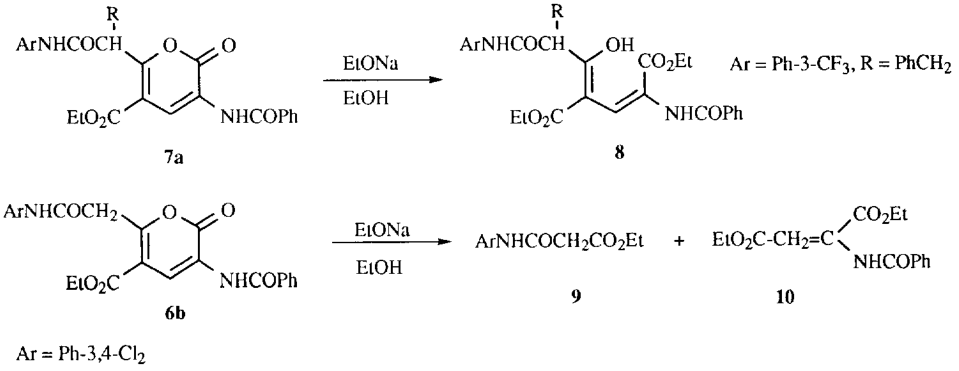
The reaction of **4** with the corresponding isocyanates **2b,e-g** in dichloromethane afforded good yields of compounds **5a-d**. The ^{1}H NMR spectra of compounds **5** strongly support their structure; important signals are found at 8.3–8.7 ppm (H–4) and at 8.3-9.4, 7.1-9.0 ppm, broad singlets, (NH, exchangeable with D_2O). The ylide structure is associated with a signal at 19 ppm in the ^{31}P NMR spectrum and at 57 ppm, $J_{C\text{-}P}$ = 132 Hz, in the ^{13}C NMR spectrum.

The reaction of **4** with aryl isocyanates **2** is an equilibrium process and affords satisfactory results only at relatively low temperature (10-15 °C) and with the more reactive isocyanates bearing electron-withdrawing groups. Aliphatic and aromatic electron-rich isocyanates gave poor results. In agreement with this picture, compounds **5** were decomposed into the starting ylide and by-products deriving from the transformation of isocyanates on heating in various solvents.

The triphenylphosphoranylidene group in compounds **5** was readily removed by reduction with zinc and acetic acid.[17] Compounds **6** were obtained in good yields. In their ^{1}H NMR spectra a significant signal is found at 4.0-4.4 ppm (CH_2).

Compounds **6** were chemoselectively C_α-monoalkylated at room temperature under solid liquid phase transfer catalysis in anhydrous dimethylformamide using potassium carbonate as non nucleophilic base[18] and triethylbenzylammonium chloride (TEBA) as catalyst yielding compounds **7** (Scheme 2). As alkylating agents benzyl and allyl bromide and methyl iodide were used. Under the conditions employed *C*-dialkylated or heteroalkylated (*N*- or *O*-) products were not found, even in the presence of an excess of the base and/or alkylating agent. In these compounds the methylenic group is a more acidic site than NH groups and for this reason it is selectively deprotonated and monoalkylated. Moreover, the absence of C_α-dialkylation probably can be explained by steric hindrance.

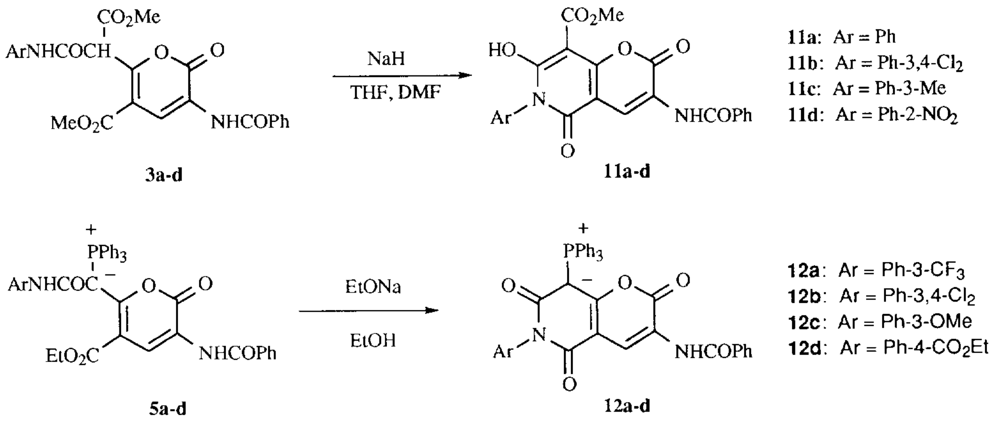
Several attempts to transform compounds **6** and **7** into the corresponding 2,5,7-trioxo-pyrano[3,2-*c*]pyridines were made under a variety of basic conditions. Unsatisfactory results were obtained in all cases with the non-nucleophilic bases K_2CO_3, *t*-BuOK, DBU, NaH and LDA in various solvents and with different substrate/base ratios; with weak bases the starting materials were recovered unchanged, whereas with strong bases intractable reaction mixtures resulted.



Scheme 3

With EtONa as nucleophilic base compound **7a** smoothly afforded the corresponding ring cleavage product **8** (Scheme 3) generated by nucleophilic attack on the lactone carbonyl group, thus confirming the reactivity of the pyrone ring toward nucleophilic reagents.[14] In the case of **6b** the reaction proceeded further giving the malonic acid derivative **9** and the substituted 2-pentenedioate **10**, both deriving, through a *retro*-Claisen process, from the primary ring opening product, analogous to **8**.

Instead, good results were obtained in the case of **3** and **5**. As shown in Scheme 4 compounds **11** and **12** were easily obtained under mild conditions.



11a: Ar = Ph
11b: Ar = Ph-3,4-Cl_2
11c: Ar = Ph-3-Me
11d: Ar = Ph-2-NO_2

12a: Ar = Ph-3-CF_3
12b: Ar = Ph-3,4-Cl_2
12c: Ar = Ph-3-OMe
12d: Ar = Ph-4-CO_2Et

Scheme 4

Amides **3** were condensed using 1 molar equivalent of sodium NaH in tetrahydrofuran/ dimethylformamide at room temperature, giving compounds **11**, whereas for compounds **5** a trace amount of sodium ethoxide in refluxing ethanol gave satisfactory yields of compounds **12**. The absence of the signals associated with the ester group and the amidic NH and the presence of a singlet associated with H-4 (8.07-8.16 ppm for **11** and 8.9 ppm for **12**) in the ^1H NMR spectra of compounds **11** and **12** confirm the formation of the pyrano-pyridine ring. It is worth noting that compounds **11** exist in the more delocalized enol structure. In fact in the ^1H NMR spectra a singlet at 12 ppm (OH, exchangeable with D_2O) is present. The presence of the ylide function in compound **12** is supported by ^{31}P NMR spectrum (14 ppm) and ^{13}C NMR spectrum (122 ppm, $J_{C\text{-}P} = 95$ Hz). Compounds **12** resisted attempts of reductive elimination of the triphenylphosphoranylidene substituent.

The failure of the cyclization reaction of compounds **6** and **7** can be explained by considering that the mechanism must involve the nucleophilic attack of the arylamide *N*-anion on the neighbouring ester group. In the present case the process may be competitive with other concurrent reactions. However in compounds **6** and **7** the highly acidic hydrogens on C_α are easily removed by bases, as confirmed by the outcome of the *C*-alkylation reaction (see above), and the acidity of NH is lower. This would oblige the use of strong bases to produce a dianion species.[19] However, strong bases and concentrated bases produce extensive deprotonation of the pyrone moiety. In the case of compounds **3** and **5** a further electronwithdrawing group is present on the C-6 substituent, thus increasing the acidity on the whole, particularly of the NH group. This allows the formation of the aza-anion in a concentration sufficient to start the cyclization reaction.[19] In the case of substrates **3** the cyclization proceeds through an initial Cα-deprotonation producing the corresponding carbanion that is in equilibrium with the Nγ-azaanion. The ring closure is probably a self-catalyzed process in which the formed methoxide anion represents the actual base. Pyrones **5** follow an analogous cyclization mechanism and only a catalytic amount of weak base is necessary, the ylide group already containing the required carbanionic species.

In conclusion, this work demonstrates the feasibility of the ring closure of arylamides of 5-alkoxycarbonyl-2-oxo-2*H*-pyran-6-acetic acids. However, this reaction is dependent on the substituents at the α-carbon which strongly affect the cyclization process.

EXPERIMENTAL

Melting points were determined using a Büchi 510 (capillary) apparatus. IR spectra were recovered on a SP Pye Unicam SP3-200S Philips spectrophotometer. NMR spectra were obtained with a Bruker AC 200 and a Varian Gemini 200 instruments. TLC: ready-to-use silica gel plates. Column chromatography: silica gel [Kieselgel 60-70 230 ASTM (Merck)] with the eluant indicated.

Material. Methyl 3-(benzoylamino)-5-(methoxycarbonyl)-2-oxo-2*H*-pyran-6-acetate **1**[16] and ethyl 3-(benzoylamino)-2-oxo-6-(triphenylphosphoranylidenemethyl)-2*H*-pyran-5-carboxylate **1**[2] are known compounds.

General Procedure for the Preparation of Methyl esters of N-Aryl-3-(benzoylamino)-5-(methoxycarbonyl)-2-oxo-2H-pyran-6-malonamides **3**. NaH (46 mg, 1.16 mmol, 60% oil suspension) was washed with anhydrous pentane (2 mL) and suspended in anhydrous THF (23 mL) under nitrogen. Pyrone **1** (400 mg, 1.16 mmol) was added and the solution was stirred at room temperature for 15 min after which a yellow solid was separated. Isocyanate **2** (1.16 mmol) was added and the mixture was stirred for the time indicated. The solvent was removed and the crude mixture was taken up with hydrochloric acid (15 mL, 10%) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with water (15 mL), dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel column (AcOEt-cyclohexane, 30:70). Compound **3** was obtained as pure solid after crystallization from CH_2Cl_2-*i*-Pr_2O. Reaction conditions and analytical data are given in Table 1, and spectroscopic data in Table 3.

General Procedure for the Preparation of N-Aryl-(triphenylphosphoranylidene)-[3-(benzoylamino)-5-(ethoxy-carbonyl)-2-oxo-2H-pyran-6]-acetamides **5**. Ylide **4** (561 mg, 1 mmol) and isocyanate (**2b,e**: 1.1 mmol; **2f**: 1.5 mmol; **2g**: 1.2 mmol) were stirred in CH_2Cl_2 (20 mL) at 10-15 °C. After the time indicated in Table 1 the solvent was evaporated *in vacuo* at 25 °C and the yellow-brown crude reaction mixture was taken up with EtOH (8 mL) and warmed (40 °C) for a few minutes until the product was dissolved. After cooling the solid was separated and filtered. The product was further purified by suspension and stirring for 15 minutes in *i*-Pr_2O (20 mL). Phosphoranes **5a-c** were isolated as pure yellow compounds. Product **5d** was obtained as an impure solid: any attempt at crystallization led to decomposition. Reaction conditions and analytical data are given in Table 1, and spectroscopic data in Table 3.

General Procedure for the Preparation of N-Aryl-3-(benzoylamino)-5-(ethoxycarbonyl)-2-oxo-2H-pyran-6-acetamides **6**. Phosphorane **5** (1 mmol) and zinc powder (2.1 g, 33 mmol) were stirred in refluxing $CHCl_3$ (30 mL). Acetic acid (10 mL) was added dropwise in 1h and the heating was continued for the time indicated. The solvent was evaporated and the sticky product was taken up with H_2O (30 mL) and extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were dried over Na_2SO_4. After solvent evaporation the crude reaction mixture was chromatographed on silica gel column with EtOAc-C_6H_6 (1:4). The acetamide **6** was obtained as pure solid after crystallization from CH_2Cl_2-*i*-Pr_2O. Reaction conditions and analytical data are given in Table 1, and spectroscopic data in Table 3.

General Procedure for the Preparation of C_α-Alkylated N-Aryl-3-(benzoylamino)-5-(ethoxycarbonyl)-2-oxo-2H-pyran-6-acetamides **7**. Pyrone **6** (0.1 mmol) was dissolved in anhydrous DMF (0.2 mL). Alkylating agent (0.11-0.13 mmol), anhydrous K_2CO_3 (11 mg, 0.11 mmol) and TEBA (2.3 mg, 0.01 mmol) were added and the mixture was stirred at room temperature for the time indicated. The solvent was evaporated and the crude reaction mixture was chromatographed on silica gel. The pure compound **7** was obtained after recrystallization. Reaction conditions and analytical data are given in Table 2, spectroscopical data are reported in Table 3.

Reaction of 7a and 6b with sodium ethoxide. Acetamide **7a** (289 mg, 0.5 mmol) was suspended and refluxed in EtOH (10 mL). A solution of EtONa in EtOH (11.5 mg, 0.5 mmol of Na in 2 mL of EtOH) was dropped in 10 min after which the starting material disappeared. The solvent was evaporated and the crude reaction mixture was chromatographed on a silica gel column (toluene/AcOEt, 70:30). Pure compound **8** (230 mg, 82 %) was isolated after recrystallization from ethyl ether. M. p.: 143 °C; IR (nujol): 3220, 1720, 1690, 1660 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.13 (3H, t, J = 7.3 Hz), 1.38 (3H, t, J = 7.3 Hz), 3.24, 3.96, 4.03 (3H, ABX system, J_{AB}= 13.8, J_{AX}= 10.9, J_{BX}= 4.4 Hz), 4.07 (2H, q, J = 7.3 Hz), 4.26 (2H, q, J = 7.3 Hz), 6.29 (1H, s), 7.2-8.2 (18 H, m), 7.94 (1H, s, exchangeable), 9.36 (1H, s, exchangeable), 13.36 (1H, s, exchangeable).

Acetamide **6b** (258 mg, 0.5 mmol) was treated as described for **7a**. The crude reaction mixture was chromatographed on a silica gel column (*n*-pentane/Et_20, 1:0 to 0:1) giving two main fractions: the first (50 mg, 36%), containing **9** the second (58 mg, 38%) containing **10**.

9: m.p. 70 °C (Found: C, 47.68; H, 3.90; N, 5.13. $C_{11}H_{11}Cl_2NO_3$ requires C, 47.83; H, 3.98, N, 5.07 %); IR (nujol): 3350, 1720, 1680 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.33 (3H, t, J = 7.1 Hz), 3.47 (2H, s), 4.26 (2H, q, J = 7.1 Hz), 7.23-8.81 (3H, m), 9.46 (1H, s, exchangeable). **10**: sticky product; ^1H NMR ($CDCl_3$): δ 1.26 (3H, t, J = 7.1 Hz), 1.33 (3H, t, J = 7.2 Hz), 3.33 (2H, d, J = 7.0), 4.18 (2H, q, J = 7.1 Hz), 4.28 (2H, q, J = 7.2 Hz), 6.94 (1H, t, J = 7.0), 7.43-7.88 (5H, m), 8.02 (1H, s, exchangeable).

General Procedure for the Preparation of Methyl 7-Aryl-3-(benzoylamino)-2,5,7-trioxo-5,6,7,8-tetrahydro-2H-pyrano[3.2-c]pyridine-8-carboxylates **11**. Compound **3** (0.4 mmol) was dissolved in anhydrous THF (10 mL) and DMF (2 mL) under nitrogen. NaH (16 mg, 0.4 mmol, 60% oil suspension) was added and the stirring was continued at room temperature for the time indicated. The solvent was evaporated, the crude mixture was taken up with HCl (10 mL, 10%) and extracted with CH_2Cl_2 (3 x 20 ml). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. Compounds **11b** and **11c** were recrystallized from AcOEt and MeOH, respectively; compounds **11a** and **11c** were chromatographed on silica gel column

(C_6H_{12}/AcOEt, 30:70 to AcOEt to AcOEt/MeOH, 20:1) and recrystallized from AcOEt and MeOH, respectively. Reaction conditions and analytical data are given in Table 2, spectroscopical data are reported in Table 3.

General Procedure for the Preparation of 7-Aryl-3-(benzoylamino)-2,5,7-trioxo-5,6,7,8-tetrahydro-2H-pyrano[3.2-c]pyridin-8-ylidenetriphenylphosphoranes **12**. Ylide **5** (1 mmol) was suspended in EtOH (25 mL) and a catalytic amount of sodium ethoxide was added. The mixture was refluxed for few min until the solid was dissolved. After 10 min the solution was cooled and compound **12** separated as a yellow solid. Reaction conditions and analytical data are given in Table 2, spectroscopic data are reported in Table 3.

Table 1. Reaction Conditions and Analytical Data for Compounds **3**, **5**, **6**, **11**, **12**.

Reagent	Time (h)	Product (Formula)	Yield (%)	m.p. °C	Calcd. % (Found) C	H	N
2a	5	**3a** ($C_{24}H_{20}N_2O_8$)	53	156	62.07 (62.31)	4.34 (4.22)	6.03 (6.36)
2b	6	**3b** ($C_{24}H_{18}Cl_2N_2O_8$)	66	160	54.05 (54.28)	3.40 (3.53)	5.25 (4.99)
2c	6	**3c** ($C_{25}H_{22}N_2O_8$)	52	166	62.75 (62.58)	4.64 (4.53)	5.86 (5.77)
2d	5	**3d** ($C_{24}H_{19}N_3O_{10}$)	79	152	56.58 (56.32)	3.76 (3.58)	8.25 (8.00)
2e	24	**5a** ($C_{42}H_{32}F_3N_2O_6P$)	80	175 (dec.)	67.37 (67.21)	4.31 (4.09)	3.74 (3.42)
2b	24	**5b** ($C_{41}H_{31}Cl_2N_2O_6P$)	85	162 (dec.)	65.69 (65.42)	4.30 (4.20)	3.74 (3.74)
2f	48	**5c** ($C_{42}H_{35}N_2O_7P$)	40	158 (dec.)	70.97 (70.70)	4.96 (5.18)	3.94 (4.08)
2g	48	**5d**	88^a				
5a	8	**6a** ($C_{24}H_{19}F_3N_2O_6$)	85	192	59.02 (58.83)	3.92 (4.12)	5.74 (5.68)
5b	8	**6b** ($C_{23}H_{18}Cl_2N_2O_6$)	83	191	56.45 (56.16)	3.71 (3.57)	5.71 (5.61)
5c	8	**6c** ($C_{24}H_{22}N_2O_7$)	80	185	63.99 (63.79)	4.92 (5.12)	6.22 (6.12)
5d	8	**6d** ($C_{26}H_{24}N_2O_8$)	71^b	194	63.40 (63.54)	4.92 (5.16)	5.69 (5.49)
3a	24	**11a** ($C_{23}H_{16}N_2O_7$)	52	309 (dec.)	63.90 (63.66)	3.73 (3.60)	6.48 (6.43)
3b	8	**11b** ($C_{23}H_{16}Cl_2N_2O_7$)	55	248 (dec.)	55.10 (55.0)	2.81 (2.77)	5.59 (5.51)
3c	48	**11c** ($C_{24}H_{18}N_2O_7$)	15	200 (dec.)	64.57 (64.39)	4.06 (3.94)	6.28 (6.07)
3e	12	**11d** ($C_{23}H_{15}N_3O_9$)	64	257 (dec.)	57.86 (57.73)	2.96 (2.88)	8.80 (8.71)
5a	0.1	**12a** ($C_{40}H_{26}F_3N_2O_5P$)	86	195	68.37 (68.61)	3.73 (3.59)	3.99 (3.79)
5b	0.1	**12b** ($C_{39}H_{25}Cl_2N_2O_5P$)	71	237	66.58 (66.37)	3.58 (3.31)	3.98 (3.93)
5c	0.1	**12c** ($C_{40}H_{29}N_2O_6P$)	70	280	72.28 (72.22)	4.40 (4.59)	4.21 (4.25)
5d	0.1	**12d** ($C_{42}H_{31}N_2O_7P$)	57^b	321 (dec.)	71.38 (71.02)	4.42 (4.68)	3.96 (3.84)

^{a} Yield on impure compound.^{b} Yield on impure starting compound.

Table 2. Reaction Conditions and Analytical Data for Compounds **7**.

Reagent	RX (mmol)	Time (h)	Chromatography[a] eluent (ratio)	Product (Formula)	Yield (%)	m.p.[c] °C	Calcd. % (Found) C	H	N
6a	$PhCH_2Br$ (0.1)	5	a (1:19)[b]	**7a** ($C_{31}H_{25}F_3N_2O_6$)	88	193-194 a	64.09 64.35	4.52 4.35	4.61 4.84
6a	MeI (0.13)	3	a (1:9)[b]	**7b** ($C_{25}H_{21}F_3N_2O_6$)	78	153-155 a	59.44 59.76	4.30 4.21	5.38 5.57
6b	$PhCH_2Br$ (0.11)	3	b (0.7:6.3:3)[b]	**7c** ($C_{30}H_{24}Cl_2N_2O_6$)	87	205-206 b	61.96 62.18	4.03 4.17	5.01 4.83
6b	MeI (0.13)	6.5	c (3:7)	**7d** ($C_{24}H_{20}Cl_2N_2O_6$)	56	202-203 b	56.98 57.27	3.98 4.00	5.72 5.57
6b	$CH_2=CHCH_2Br$ (0.12)	4	d (1:1)	**7e** ($C_{26}H_{22}Cl_2N_2O_6$)	70	168-169 b	58.84 58.98	4.13 4.19	5.49 5.29

[a]a: Et_2O-C_6H_6; b: Et_2O-C_6H_6-pentane; c: AcOEt-cyclohexane; d: AcOEt-C_6H_6. [b]Flash chromatography [c] a: CH_2Cl_2-Et_2O; b: CH_2Cl_2-$i$$Pr_2O$

Table 3. Spectroscopic Data for Compounds **3**, **5-7**, **11**, **12**.*

	ν_{max}/cm^{-1} [a]		δ_H($CDCl_3$), (J /Hz)			
Product	NH	C=O	NH	H-4	Arom.	Other
3a	3280, 3250	1760, 1740, 1720, 1650	9.9, 8.6	8.9	7.9-7.1	5.6 (s, CH), 3.89, 3.82 (CO_2Me)
3b	3290, 3250	1760, 1740, 1720, 1650	10.0, 8.6	8.9	7.9-7.5	5.5 (s, CH), 3.88, 3.81 (CO_2Me)
3c	3280, 3260	1760, 1740, 1720, 1650	9.8, 8.6	8.9	7.9-6.9	5.6 (s, CH), 3.88, 3.82 (CO_2Me), 2.3 (s, Me)
3d	3400, 3250	1740, 1720, 1700, 1660 [b]	10.8, 9.9	8.5	8.1-7.4	5.9 (s, CH), 3.88, 3.78 (CO_2Me)
5a	3380, 3330	1710, 1700, 1640 [b]	9.3, 9.0	8.3	8.1-7.4	4.0, 1.1 (CO_2Et)
5b	3380, 3350	1720, 1700, 1680, 1640 [b]	9.4, 9.0	8.3	7.9-7.3	4.0, 1.1 (CO_2Et)
5c	3380, 3320	1720, 1680, 1650	8.3, 7.1	8.8	7.9-6.4	4.2, 1.2 (CO_2Et), 3.7 (s, OMe)
5d	3400-3250	1720, 1700, 1690, 1640	8.3, 7.6	8.7	8.1-7.4	4.2, 1.2 (CO_2Et)
6a	3380, 3350	1730, 1710, 1670, 1640	8.9, 8.6	8.8	7.9-7.3	4.4, 1.4 (CO_2Et), 4.0 (s, CH_2)
6b	3290	1720, 1700, 1660	8.9, 8.6	8.8	7.9-7.3	4.4, 1.4 (CO_2Et), 4.1 (s, CH_2)
6c	3390, 3350	1720, 1700, 1680, 1660	8.6	8.8	7.9-6.6	4.4, 1.4 (CO_2Et), 4.0 (s, CH_2), 3.7 (s, OMe)
6d	3400, 3390	1720, 1700, 1670, 1660	9.0, 8.6	8.85	8.0-7.5	4.4, 1.44 (CO_2Et), 4.3, 1.38 (CO_2Et), 4.0 (s, CH_2)

7a	3300, 3280, 3200, 3150	1740, 1710, 1690, 1650	9.1, 8.6	8.7	7.9-7.2	4.92[c] (CH), 4.4, 1.4 (CO_2Et), 3.56, 3.39 (CH_2)[c]
7b	3400, 3320 3270	1720, 1710, 1680, 1660	9.4, 8.6	8.8	7.9-7.3	4.67[d] (CH), 4.5, 1.5 (CO_2Et), 1.6 (Me)[d]
7c	3390, 3300 3270	1720, 1690, 1680	9.1, 8.6	8.7	7.9-7.2	4.86[e] CH), 4.4, 1.4 (CO_2Et), 3.66, 3.45 (CH_2)[e]
7d	3400, 3280	1720, 1700, 1680, 1660	9.3, 8.6	8.8	7.9-7.3	4.67[f] (CH), 4.5, 1.5 (CO_2Et), 1.6 (Me)[f]
7e	3280, 3250, 3160	1730, 1710, 1650, 1660	9.3, 8.6	8.8	7.9-7.3	4.59 (CH), 5.8-5.7 (m, CH=), 5.2-5.0 (m, CH_2=), 4.5, 1.5 (CO_2Et), 2.99-2.74 (CH_2)
11a	3610-3220	1730, 1670, 1620	[b] 9.4	8.1	8.0-7.1	12.0 (s, OH), 3.7 (s, Me)
11b	3360	1690, 1630	[b] 9.4	8.1	8.0-7.1	12.0 (s, OH), 3.7 (s, OMe)
11c	3390	1720,1670,1620	[b] 9.4	8.1	8.0-6.8	9.0 (s, OH), 3.6 (s, OMe), 2.3 (s, Me)
11e	3350	1730,1690, 1640	9.4	8.1	8.2-7.4	12.0 (s, OH), 3.7 (s, OMe)
12a	3380	1720,1670	8.1	8.9[g]	7.8-7.3	
12b	3390	1720,1670	8.1	8.9[g]	7.8-7.0	
12c	3350	1720,1660	8.1	8.9[h]	7.8-6.7	3.7 (s, OMe)
12d	3400	1710,1680, 1650	8.1	8.9[g]	8.1-7.3	4.3, 1.3 (CO_2Et)

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[a] Nujol. [b] DMSO-d_6. [c] ABX system, J_{AB} 14.11, J_{AX} 7.45, J_{BX} 7.89. [d] AX_3 system, J_{AX} 7.8. [e] ABX system, J_{AB} 14.07, J_{AX} 7.65, J_{BX} 7.73. [f] AX_3 system, J_{AX} 6.7. [g] d, J 1.5. [h] d, J 1.6.

* *Appendix*: δ_C ($CDCl_3$) **3b**: 53.27, 53.39 (OMe), 56.96 (CH), 111.31 (C-5), 119.69, 120.88 (C arom) 124.08 (C-3), 125.89, 131.52 (C arom), 126.78 (C-4), 128.08-132.61, 133.59, 138,63 (C arom), 156.54, 156.98, 162.86, 163.85, 166.36, 166.59 (C-6 and CO). **5d**: 14.7, 14.8 (Me), 57.5 (d, $J_{C\text{-}P}$ 132.7, C-P), 60.9, 62.1 (OCH_2), 112.0 (d, $J_{C\text{-}P}$ 7.8, C-5), 120.7 (C-3), 126.1 (d, $J_{C\text{-}P}$ 93.1, C arom), 127.5 (C-4), 124-134, 144.1, 144.7 (C arom), 159.1 (d, $J_{C\text{-}P}$ 6.5, C-6), 165.5, 166.2, 166.8, 166.9, 167.0 (C=O). **11a**: 50.9 (Me), 88.3 (C-8), 93.8 (C-4a), 111.05 (C-3), 126.95-131.60, 133.87 137.74 (C arom and C-4), 158.54, 160.45, 161.20, 161.96,165.41, 165.74 (C=O, C-7, C-8a). **12d**: 14.8 (Me), 61.3 (OCH_2), 65.5 (d, $J_{C\text{-}P}$ 127, C-8), 98.4 (d, $J_{C\text{-}P}$ 7.9, C-4a), 115.9 (C-3), 123.0 (d, $J_{C\text{-}P}$ 94.8, C arom), 124.3-133.8, 134.1, 140.8 (C arom and C-4), 158.3, 162.5, 163.9, 165.5, 166.5 (C=O, C-7 and C-8a). δ_P ($CDCl_3$) **5d**: 19.01. **12d**: 14.17.

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(*Received in UK* 25 *November* 1994; *revised* 10 *January* 1995; *accepted* 13 *January* 1995)