Brief Communications

Synthesis of 2- and 3-pyridinyl(aryl)methanones

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A procedure was developed for the preparation of 2- and 3-pyridinyl(aryl)methanones by the reactions of aryllithium with methyl pyridinecarboxylate and methyl esters of substituted phenylcarboxylic acids.

Key words: aryl(pyridinyl)methanones, 2-pyridinyllithium, 3-pyridinyllithium, 4-methoxyphenyllithium, acylation.

Pyridinyl(aryl)methanones are promising synthons in the synthesis of physiologically active compounds.

The aim of the present study was to develop a general procedure for the synthesis of 2- and 3-pyridinyl(aryl)methanones containing different, including acid-labile, substituents.

Among procedures for the synthesis of phenyl(pyridinyl)methanones, methods based on the use of organomagnesium[1—6] or organolithium compounds[1,2,7—9] show the most promise.

Attempts to prepare ketones containing acid-labile substituents in the aromatic nucleus by treating aromatic nitriles with a solution of pyridinyllithium[2,7—8] failed because rather harsh conditions of subsequent acid hydrolysis of intermediate ketimines led to elimination of these groups.

Our concern was to find conditions of condensation precluding acid hydrolysis of the final products. We used methyl esters of aromatic acids as acylating agents. Previously, phenyl(2-pyridinyl)methanone has been synthesized in 71% yield by the reaction of BzOMe with a solution of 2-pyridinyllithium in THF at −100 °C.[9]

Preliminary experiments based on an analogous approach demonstrated that lowering of the reaction temperature as well as the reverse order of addition of the reagents led to an increase in the yield of the target ketone and a decrease in the yields of by-products. We found solvents and reaction temperatures, which ensure solubility of the components, the desired direction of condensation, and the maximum yields of the target compounds. For this purpose, we prepared 2(3)-pyridinyllithium by adding a solution of Bu^nLi in hexane, which was cooled to −90 °C, to a solution of 2- (**1**) or 3-bromopyridine (**2**) in a mixture of THF and Et_2O cooled to the same temperature. Then the reaction mixture was cooled to −110 °C and treated with a solution of methyl ester of substituted benzoic acid in toluene. Subsequent mild decomposition of the resulting complex with an aqueous solution of NH_4Cl was not accompanied by elimination of the methoxymethyl group. These modifications allowed us to

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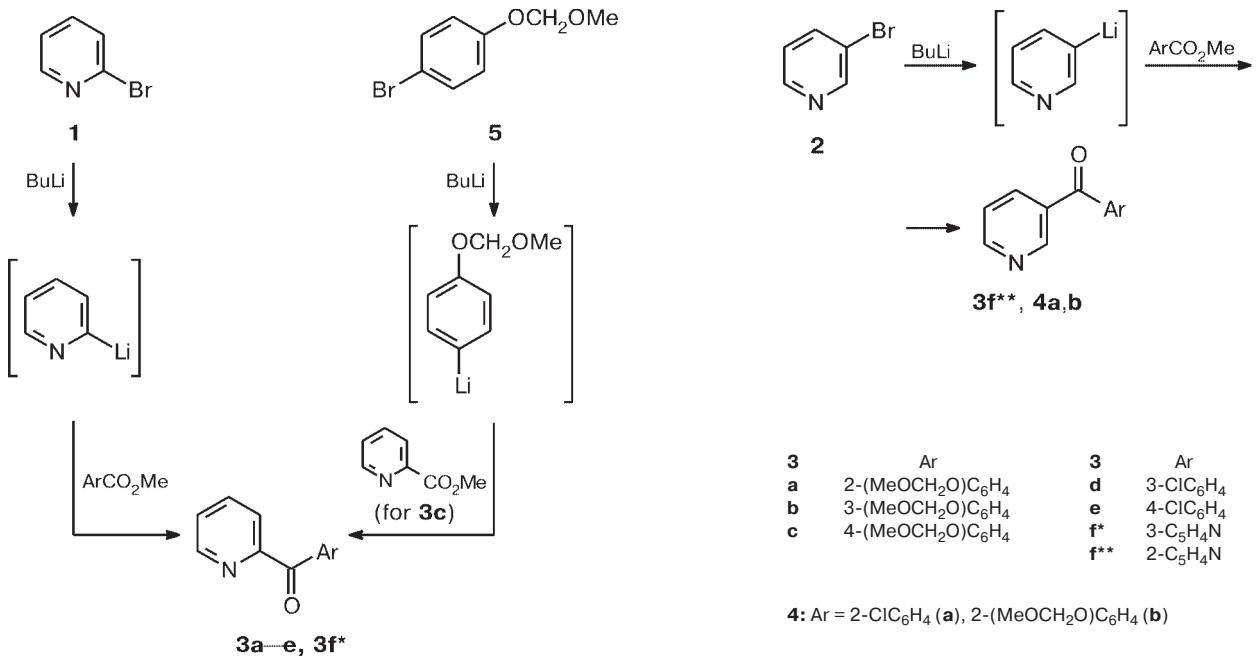
Scheme 1



3	Ar	3	Ar
a	2-(MeOCH$_2$O)C$_6$H$_4$	d	3-ClC$_6$H$_4$
b	3-(MeOCH$_2$O)C$_6$H$_4$	e	4-ClC$_6$H$_4$
c	4-(MeOCH$_2$O)C$_6$H$_4$	f*	3-C$_5$H$_4$N
		f**	2-C$_5$H$_4$N

4: Ar = 2-ClC$_6$H$_4$ (**a**), 2-(MeOCH$_2$O)C$_6$H$_4$ (**b**)

simplify the preparation of compounds **3e** and **4a**, which have been described earlier, and to synthesize previously unavailable compounds **3a—d**,**f** and **4b** (Scheme 1, Table 1).

When performing the synthesis of compound **3f**, we found that the use of 3-bromopyridine for the preparation of the corresponding organolithium compound and its subsequent acylation with methyl pyridine-2-carboxylate afforded compound **3f** in 89% yield, whereas the use of 2-bromopyridine and methyl pyridine-3-carboxylate allowed the preparation of compound **3f** in only 60% yield. We believe that this fact is associated both with the higher reactivity of 3-pyridinyllithium compared to the corresponding 2-substituted derivative and the higher electrophilicity of the carbonyl component, *viz.*, methyl pyridine-2-carboxylate.

The above-considered scheme, as applied to the synthesis of compound **3c**, proved to be a poor choice. Thus the reaction afforded a mixture of compounds from which the target compound was isolated in low yield. Because of this, we devised an alternative procedure for the synthesis of compound **3c** involving the preparation of the organolithium compound from 1-bromo-4-(methoxymethoxy)benzene (**5**) under the above-described conditions followed by its treatment with a solution of methyl pyridine-2-carboxylate. In this case, compound **3c** was obtained in virtually quantitative yield. Apparently, 2-pyridinyllithium not only attacks the carbonyl carbon atom but also is sufficiently nucleophilic that it cleaves the methoxymethyl group in the *para* position.

The structures of the resulting compounds were established by ^{1}H NMR spectroscopy (Table 2) and confirmed by the data from elemental analysis (Table 1) and mass spectrometry. The assignments of the signals in the ^{1}H NMR spectra are consistent with those made based on simulation of the ^{1}H NMR spectra with the use of the ACD Labs program.

Experimental

The ^{1}H NMR spectra were recorded on a Bruker AMX-400 spectrometer (^{1}H, 400 MHz) in DMSO-d$_6$ relative to the residual protons of the solvents. The melting points were determined on a Boetius hot stage (the rate of heating was 4 deg min^{-1}). The mass spectra were obtained on a Kratos MS-30 spectrometer (EI, 70 eV). The reactions were carried out under an atmosphere of dry nitrogen. The solvents were thoroughly purified and dried before use. A 1.5 *M* solution of Bu^{n}Li in hexane (Merck), 2- and 3-bromopyridines, methyl 2-chlorobenzoate, methyl 3-chlorobenzoate, and methyl 3-pyridinecarboxylate (all reagents were from Aldrich) were used. Methyl 2-pyridinecarboxylate was synthesized according to a known procedure.[11] 1-Bromo-4-(methoxymethoxy)benzene and methyl esters of 2-, 3-, and 4-(methoxymethoxy)benzoic acids were prepared according to a procedure described previously.[12]

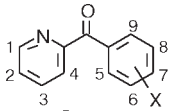
Synthesis of 2- and 3-pyridinyl(aryl)methanones (3a—f and 4a—b) (general procedure). A 1.5 *M* solution of Bu^{n}Li in hexane (200 mL) was added to a solution of 2- or 3-bromopyridine (**1** or **2**) (47.4 g, 0.3 mol) in a mixture of THF (100 mL) and Et$_2$O (150 mL) at −90 °C under an inert atmosphere. The reaction mixture was stirred at −90 °C for 15 min and cooled to −110 °C. Then a solution of methyl ester of substituted benzoic acid or

Table 1. Yields, melting points, and data from elemental analysis of the resulting compounds

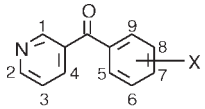
Compound	Yield (%)	M.p./°C	Found / Calculated (%)				Molecular formula
			C	H	N	Cl	
3a	73	Oil	69.12 69.13	5.49 5.39	5.72 5.76	—	$C_{14}H_{13}NO_3$
3b	71	Oil	69.12 69.13	5.49 5.39	5.72 5.76	—	$C_{14}H_{13}NO_3$
3c	43 [a] 96 [b]	Oil	68.95 69.13	5.30 5.39	5.55 5.76	—	$C_{14}H_{13}NO_3$
3d	86	79	66.51 66.22	4.01 3.71	6.45 6.44	16.18 16.29	$C_{12}H_8ClNO$
3e	78	65 (65—66)[10]	—	—	—	—	—
3f	60 [c] 89 [d]	68	71.81 71.73	4.38 4.38	15.21 15.21	—	$C_{11}H_8N_2O$
4a	60	Oil (50)[2]	66.16 66.22	3.70 3.71	6.23 6.44	16.45 16.29	$C_{12}H_8ClNO$
4b	70	62	69.12 69.13	5.28 5.39	5.77 5.76	—	$C_{14}H_{13}NO_3$

[a] The yield of **3c** prepared according to the general procedure.
[b] The yield of **3c** prepared according to the specially devised procedure.
[c] 2-Pyridinyllithium and methyl pyridine-3-carboxylate were used.
[d] 3-Pyridinyllithium and methyl pyridine-2-carboxylate were used.

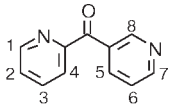
Table 2. Data from ^{1}H NMR spectroscopy for the resulting compounds



3a—e



4a,b



3f

Compound	^{1}H NMR (DMSO-d_6, J/Hz)
3a	8.63 (d, 1 H, H(1), J = 5.2); 8.03 (dd, 1 H, H(3), J = 7.0, J = 5.5); 7.98 (d, 1 H, H(4), J = 7.0); 7.62 (dd, 1 H, H(2), J = 5.5, J = 5.2); 7.49 (dd, 1 H, H(7), J = 7.0, J = 7.0); 7.41 (d, 1 H, H(5), J = 7.0); 7.18 (d, 1 H, H(8), J = 7.0); 7.10 (dd, 1 H, H(6), J = 7.0, J = 7.0); 5.50 (s, 2 H, OCH_2O); 3.10 (s, 3 H, OCH_3)
3b	8.72 (d, 1 H, H(1), J = 4.8); 8.06 (dd, 1 H, H(3), J = 5.0, J = 7.2); 7.98 (d, 1 H, H(4), J = 7.2); 7.67 (dd, 1 H, H(2), J = 4.8, J = 5.0); 7.60 (d, 1 H, H(5), J = 8.2); 7.47 (dd, 1 H, H(6), J = 8,2, J = 8.2); 7.33 (d, 1 H, H(7), J = 8.2); 5.30 (s, 2 H, OCH_2O); 3.40 (s, 3 H, OCH_3)
3c	8.72 (d, 1 H, H(1), J = 8.3); 8.06 (dd, 1 H, H(2), J = 8.3, J = 8.5); 8.00 (d, 2 H, H(5,9), J = 8.6); 7.94 (d, 1 H, H(4), J = 9.3); 7.64 (dd, 1 H, H(3), J = 8.5, J = 9.3); 7.15 (d, 2 H, H(6,8), J = 8.6); 5.30 (s, 2 H, OCH_2O); 3.40 (s, 3 H, OCH_3)
3d	8.74 (d, 1 H, H(1), J = 3.7); 8.09 (dd, 1 H, H(3), J = 4.0, J = 6.7); 8.07 (d, 1 H, H(5), J = 6.7); 8.0 (s, 1 H, H(8)); 7.93 (d, 1 H, H(7), J = 8.3); 7.75 (d, 1 H, H(4), J = 6.7); 7.71 (dd, 1 H, H(2), J = 3.7, J = 4.0); 7.58 (dd, 1 H, H(6), J = 6.7, J = 8.3)
3e	8.72 (d, 1 H, H(1), J = 4.5); 8.06 (dd, 1 H, H(3), J = 6.2, J = 7.4); 8.01 (d, 1 H, H(4), J = 7.4); 8.00 (d, 2 H, H(5), H(9), J = 8.3); 7.70 (dd, 1 H, H(2), J = 5,7, J = 6.2); 7.62 (d, 2 H, H(6), H(8), J = 8.3)
3f	9.14 (s, 1 H, H(8)); 8.82 (d, 1 H, H(7), J = 4.0); 8.75 (d, 1 H, H(1), J = 4.5); 8.35 (d, 1 H, H(3), J = 7.4); 8.12 (br.s, 1 H, H(4)); 8.15 (br.s, 1 H, H(5)); 7.73 (dd, 1 H, H(2), J = 4.5, J = 7.4); 7.57 (d, 1 H, H(6), J = 4.0)
4a	8.85 (d, 1 H, H(2), J = 6.3); 8.84 (s, 1 H, H(1)); 8.10 (d, 1 H, H(4), J = 7.4); 7.50—7.65 (m, 5 H, H(3), H(5), H(6), H(7), H(8))
4b	8.83 (br.s, 1 H, H(1)); 8.79 (d, 1 H, H(2), J = 4.2); 8.06 (d, 1 H, H(4), J = 7.0); 7.58 (dd, 1 H, H(7), J = 8.0, J = 9.3); 7.43 (d, 1 H, H(5), J = 8.0); 7.26 (d, 1 H, H(8), J = 9.3); 7.19 (dd, 1 H, H(6), J = 8.0, J = 8.0); 5.10 (s, 2 H, OCH_2O); 3.15 (s, 3 H, OCH_3)

the corresponding methyl pyridinecarboxylate (0.3 mol) in toluene (100 mL) was added and the cooling bath was removed. After 4 h, a saturated solution of NH_4Cl (200 mL), water (400 mL), and AcOEt (400 mL) were successively added to the reaction mixture. The organic layer was separated, washed with water (2×400 mL) and a saturated solution of NaCl (400 mL), and dried over Na_2SO_4. The solvent was evaporated. Compounds **3d**—**f** and **4b** were recrystallized from hexane. Compounds **3a**—**c** and **4a** were isolated by chromatography on a column with silica gel (a 95 : 5 benzene—acetone mixture as the eluent).

[4-(Methoxymethoxy)phenyl](2-pyridinyl)methanone (3c). A 1.5 *M* solution of Bu^nLi in hexane (200 mL) was added to a solution of 1-bromo-4-(methoxymethoxy)benzene[11] (**5**) (65.1 g, 0.3 mol) in a mixture of THF (100 mL) and Et_2O (150 mL) at −90 °C. The reaction mixture was stirred at −90 °C for 15 min and cooled to −110 °C. Then a solution of methyl pyridine-2-carboxylate (41.1 g, 0.3 mol) in toluene (100 mL) was added and the cooling bath was removed. After 4 h, a saturated solution of NH_4Cl (200 mL), water (400 mL), and AcOEt (400 mL) were successively added to the reaction mixture. The organic layer was separated, washed with water (2×400 mL) and a saturated solution of NaCl (400 mL), and dried over Na_2SO_4. The solvent was evaporated. Compound **3c** was purified by chromatography on a column with silica gel (a 95 : 5 benzene—acetone mixture as the eluent). Compound **3c** was isolated as a colorless oil in a yield of 70.0 g (96%).

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