SYNTHESIS OF 2-AROYLQUINOXALINES, 1-AROYLPHTHALAZINES, AND 4-AROYLCINNOLINES; AN AROYLATION METHOD USING ARENECARBALDEHYDES CATALYZED BY AZOLIUM SALT [1]

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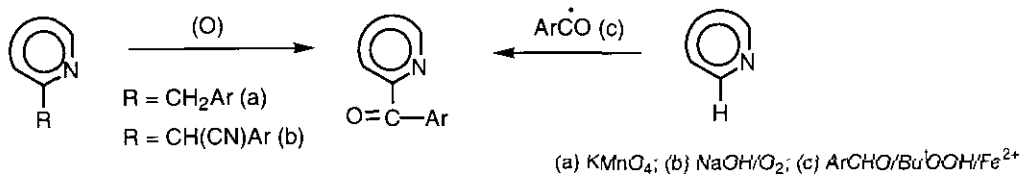
Abstract — 2-Aroylquinoxalines (**5**, **6**), 1-aroylphthalazines (**10**, **11**), and 4-aroylcinnolines (**13**) were synthesized by using arenecarbaldehydes (**2**) in the presence of an azolium salt (**1**) in moderate to good yields. 1,3-Dimethylimidazolium iodide (**1a**) and sodium sulfinate (**7**) were also effective catalysts in this aroylation.

In our studies on the synthesis and reactivities of fused diazines,[2] our interest has been focused on the synthesis of ketones having the benzodiazine ring system. Many naturally occurring fused diazine derivatives such as fused pyrimidines and fused pyrazines, have interesting biological activities.[3] However, no systematic method of introducing aroyl groups into benzodiazines has yet been established.

A few preparative methods for benzodiazines having an acyl group have been reported. A benzyl group and an α-cyanobenzyl group are easily converted to an aroyl group under oxidative conditions.[4] Further, acylquinoxalines were synthesized by homolytic acylation using acyl radical obtained from aldehyde.[5] However, the yields of the aroylheteroarenes obtained by these methods are low and handling is troublesome.

We have already presented a catalytic aroylation method using arenecarbaldehydes (**2**) as the aroyl sources, by

Scheme 1

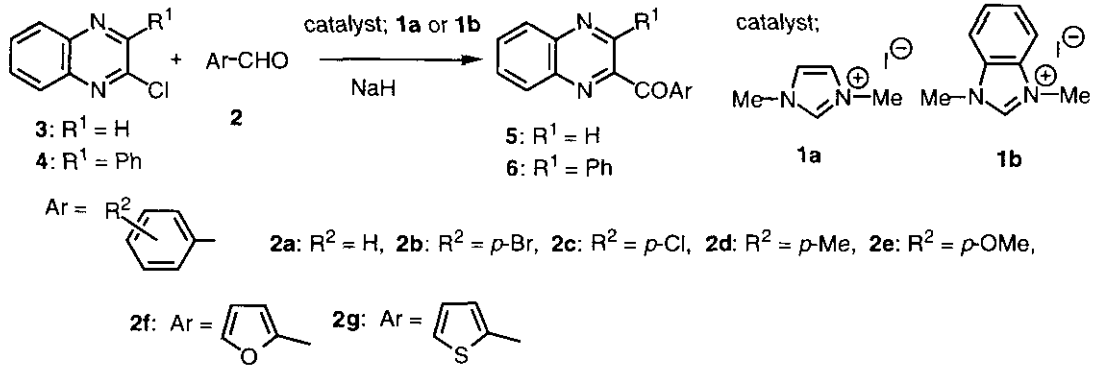


(a) $KMnO_4$; (b) $NaOH/O_2$; (c) $ArCHO/Bu^tOOH/Fe^{2+}$

means of which the aroyl groups can be nucleophilically introduced into heteroarenes in the presence of azolium salts (**1a**, **1b**) as catalysts.[6] We confirmed that this is a facile method of synthesizing aroylheteroarenes. These

results led us to synthesize new aroylbenzodiazines by means of catalytic aroylation. In this paper, we wish to describe the synthesis of 2-aroylquinoxalines (**5**, **6**), 1-aroylphthalazines (**10**, **11**), and 4-aroylcinnolines (**13**). In the presence of 1,3-dimethylbenzimidazolium iodide (**1b**), 2-chloroquinoxaline (**3**) reacted with benzaldehyde (**2a**) in THF to give 2-benzoylquinoxaline (**5a**), though the yield was low (12 %). In contrast, the use of 1,3-dimethylimidazolium iodide (**1a**) afforded the ketone (**5a**) in good yield (82 %). Further, it seemed that DMF is an effective solvent. We tried to synthesize other aroylquinoxalines (**5**, **6**), and the corresponding ketones were obtained in moderate yields, as shown in Scheme 2.

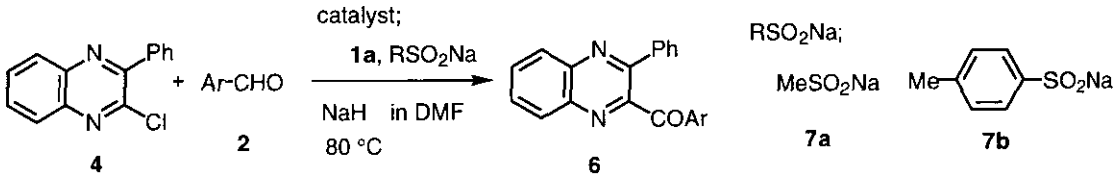
Scheme 2



	Reaction Conditions					Ketone (**5**, **6**)	
3 or **4**	Aldehyde	Catalyst	Solvent	Temp	Time (min)		Yield (%)(recovery)
3	**2a**	**1a**	THF	Reflux	30	**5a**	82
3	**2a**	**1b**	THF	Reflux	30	**5a**	12 (32)
3	**2a**	**1a**	DMF	80 °C	15	**5a**	85
3	**2c**	**1a**	THF	Reflux	30	**5c**	54
3	**2e**	**1a**	THF	Reflux	30	**5e**	61
4	**2a**	**1a**	THF	Reflux	30	**6a**	5 (59)
4	**2a**	**1a**	DME	Reflux	120	**6a**	54
4	**2c**	**1a**	DMF	80 °C	10	**6c**	76
4	**2e**	**1a**	DME	Reflux	60	**6e**	80

We have already reported that sodium *p*-toluenesulfinate (**7b**) acts as an effective catalyst in KCN–catalyzed aroylation due to the *in situ* formation of *p*-tosylheteroarenes.[7] The fact that the treatment of **4** with **7b** in DMF gave 2-tosyl-3-phenylquinoxaline indicates that sodium sulfinate (**7**) similarly acts as an effective catalyst in the aroylation of **4**.[8] We employed this method in imidazolium salt–catalyzed aroylation. As shown in Scheme 3, in the presence of an catalytic amount of sodium sulfinate (**7**), the 2-aroylquinoxalines (**6**) were obtained in good yields.

Scheme 3

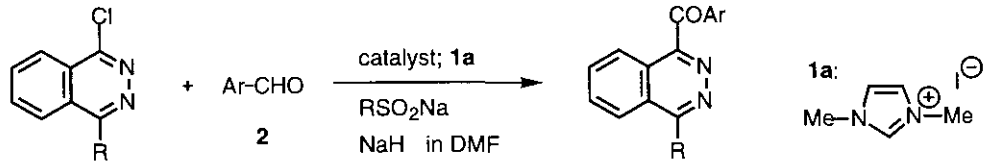


Reaction Conditions			Ketone (6)	
Aldehyde	RSO_2Na	Time (min)		Yield (%) (recovery)
2a	**7a**	10	**6a**	96
2a	**7b**	10	**6a**	87
2a	–	10	**6a**	7 (85)
2c	**7a**	10	**6c**	94
2d	**7a**	15	**6d**	90
2e	**7a**	10	**6e**	97
2e	**7b**	10	**6e**	97
2f	**7b**	15	**6f**	78
2g	**7b**	15	**6g**	69

The aroylation method utilizing the double catalytic actions of imidazolium salt (**1a**) and sodium sulfinate (**7a** or **7b**) was employed to synthesize 2-aroylphthalazines (**10**, **11**) and 4-aroylcinnolines (**13**).

In the presence of catalytic amounts of sodium *p*-toluenesulfinate (**7b**) and imidazolium salt (**1a**), 1-chlorophthalazine

Scheme 4



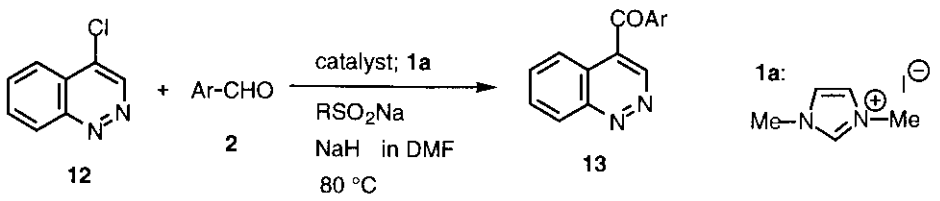
8: R = Ph
9: R = *Me*

10: R = Ph
11: R = Me

	Reaction Conditions			Ketone (**10**)	
	Aldehyde	RSO_2Na	Time (min)		Yield (%) (recovery)
8	**2a**	**7b**	20	**10a**	63
8	**2a**	**7a**	20	**10a**	79
8	**2a**	–	20	**10a**	– (67)
8	**2b**	**7b**	15	**10b**	63
8	**2c**	**7b**	15	**10c**	63
8	**2d**	**7b**	30	**10d**	50
8	**2e**	**7b**	15	**10e**	95
8	**2f**	**7b**	10	**10f**	50
8	**2g**	**7b**	40	**10g**	53
9	**2d**	**7b**	10	**11d**	60

(**8**, **9**) reacted with arenecarbaldehydes (**2**) to give 1-aroylphthalazines (**10**, **11**) in moderate to good yields. 4-Aroylcinnolines (**13**) were similarly synthesized in moderate yields. These results are shown in Schemes 4 and 5. We have shown that the imidazolium salt (**1a**) and sodium sulfinate (**7**) are effective catalysts in this aroylation.

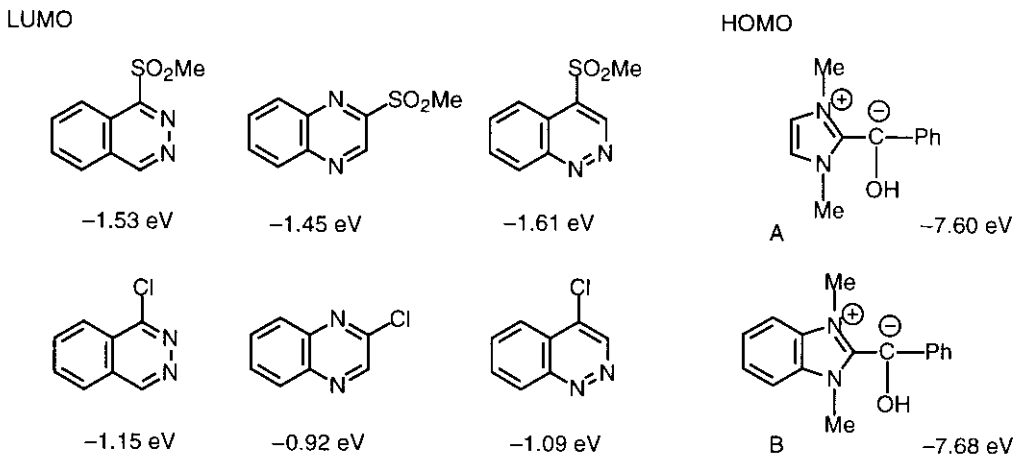
Scheme 5



Aldehyde	Reaction Conditions RSO_2Na	Time (min)	Ketone (**13**)	Yield (%)
2a	**7b**	10	**13a**	73
2a	–	10	**13a**	39
2c	**7b**	10	**13c**	68
2c	–	10	**13c**	36
2d	**7b**	10	**13d**	53
2e	**7a**	15	**13e**	75
2e	–	15	**13e**	63
2f	**7b**	15	**13f**	48
2g	**7b**	15	**13g**	61

The mechanism involving double catalytic actions has already been described in the previous paper.[7] The formation of the sulfonylbenzodiazines and the nucleophilic substitution with the intermediate (A or B) are the key steps in this aroylation. The calculated HOMOs and LUMOs for the key intermediates are consistent with the facts that methylsulfonylheteroarenes are more easily converted to aroylheteroarenes than chloroheteroarenes,

Scheme 6



because the LUMOs of the methylsulfonylheteroarenes are lower than those of the corresponding chloroheteroarenes. In conclusion, an efficient synthetic method of 2-aroylquinoxalines (**5**, **6**), 1-aroylphthalazines (**10**, **11**), and 4-aroylcinnolines (**13**) *via* imidazolium salt–catalyzed aroylation was established. Sodium sulfinates (**7a**, **b**) were also effective catalysts

EXPERIMENTAL

All melting points were measured without correction. IR spectra were recorded on a JASCO A-102 diffraction grating IR spectrophotometer. ^{1}H-NMR spectra were measured at 60 MHz on a JEOL PMX60SI NMR spectrometer and at 270 MHz on a JEOL JNM-GSX270 FT-NMR spectrometer. Chemical shifts are quoted in parts per million (ppm) with tetramethylsilane as an internal standard, and coupling constants (*J*) are given in Hz. Calculations for HOMOs and LUMOs were performed by MOPAC Ver 6.0 (PM3) on a CAChe system (SONY Tektronix).

Reaction of 2-Chloroquinoxaline (3, 4) with an Arenecarbaldehyde (2) Catalyzed by Azolium Salt (1a, 1b). General Procedure

Sodium hydride (60% in oil, 144 mg, 3.6 mmol) was added to a solution of 2-chloroquinoxaline (**3** or **4**, 3.0 mmol), an arenecarbaldehyde (**2**, 3.6 mmol), and an azolium salt [1,3-dimethylimidazolium iodide (**1a**): 224 mg (1.0 mmol), 1,3-dimethylbenzimidazolium iodide (**1b**): 274 mg (1.0 mmol)] in 20 mL of THF (or DME) and the mixture was refluxed for 30 min with stirring. The reaction mixture was poured into ice-H_2O, neutralized with AcOH, and extracted with $CHCl_3$. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on SiO_2 with benzene then $CHCl_3$. The fraction eluted with $CHCl_3$ gave the ketone (**5**, **6**). In the case of the DMF as the reaction solvent, the reaction was carried out at 80 °C and AcOEt was used as the extraction solvent. The results are shown in Scheme 2.

Reaction of 2-Chloroquinoxaline (4) with an Arenecarbaldehyde (2) Catalyzed by Imidazolium Salt (1a) and Sodium Sulfinate (7a or 7b). General Procedure

Sodium hydride (60% in oil, 144 mg, 3.6 mmol) was added to a solution of 2-chloroquinoxaline (**4**, 3.0 mmol), 1,3-dimethylimidazolium iodide (**1a**, 224 mg 1.0 mmol), and sodium sulfinate [sodium methanesulfinate (**7a**): 102 mg (1.0 mmol) or sodium *p*-toluenesulfinate (**7b**): 178 mg (1.0 mmol)] in 20 mL of DMF and the mixture was stirred at 80 °C. The reaction mixture was poured into ice-H_2O, neutralized with AcOH, and extracted with AcOEt. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on SiO_2 with benzene then $CHCl_3$. The fraction eluted with $CHCl_3$ gave the ketone (**6**).

Table 1. Appearance, Recrystallization Solvent, Melting Point, and Elemental Analyses for 2-Aroylquinoxalines (**5**, **6**), 1-Aroylphthalazines (**10**, **11**), and 4-Aroycinnolines (**13**).

Compd	mp (°C)	Appearance (Recrystallization solvent)	Formula	Analysis (%); Calcd (Found) C	H	N
5a	77–79 (lit.,[5a] 80–81)	Yellow needles (benzene–petroleum benzin)	$C_{15}H_{12}N_2O_2$			
5c	111–112.5 (lit.,[5a] 105)	Yellow needles (benzene–petroleum benzin)	$C_{15}H_{11}N_2O_2Cl$			
5e	113 (lit.,[5a] 113)	Yellow needles (benzene–petroleum benzin)	$C_{15}H_{11}N_2O_2Cl$			
6a	154–155	Slightly yellow prisms (benzene-petroleum benzin)	$C_{21}H_{14}N_2O$	81.27 (81.23)	4.55 (4.53)	9.03 (8.87)
6b	158–159	Slightly brown granules (benzene-petroleum benzin)	$C_{21}H_{13}N_2OBr$	64.80 (65.00)	3.37 (3.30)	7.20 (6.94)
6c	161–162.5	Colorless prisms (petroleum benzin)	$C_{21}H_{13}N_2OCl$	73.15 (73.14)	3.80 (3.77)	8.12 (8.08)
6d	163–165	Yellow prisms (petroleum benzin)	$C_{22}H_{16}N_2O$	81.46 (81.13)	4.97 (5.10)	8.64 (8.35)
6e	132–133	Colorless prisms (MeOH)	$C_{22}H_{16}N_2O_2$	77.63 (77.27)	4.74 (4.79)	8.23 (8.16)
6f	136–137	Brown prisms (MeOH)	$C_{19}H_{12}N_2O_2$	75.99 (75.78)	4.03 (3.89)	9.33 (9.35)
6g	132–133	Slightly brown prisms (MeOH)	$C_{19}H_{12}N_2OS$	72.13 (72.20)	3.82 (3.77)	8.85 (8.88)
10a	134–136	Yellow prisms (MeOH)	$C_{21}H_{14}N_2O$	64.46 (64.18)	4.16 (4.11)	11.56 (11.42)
10b	157–158	Yellow powder (MeOH)	$C_{17}H_{14}N_2O_2Br$	73.37 (73.23)	5.07 (5.12)	10.07 (10.03)
10c	151–153	Yellow prisms (MeOH)	$C_{21}H_{13}N_2OCl$	73.15 (73.20)	3.80 (3.79)	8.12 (7.94)
10d	129–130	Yellow needles (benzene-petroleum benzin)	$C_{17}H_{14}N_2O$	77.84 (77.48)	5.38 (5.30)	10.68 (10.41)
10e	146–146.5	Yellow prisms (MeOH)	$C_{22}H_{16}N_2O_2$	77.63 (77.39)	4.74 (4.70)	8.23 (8.11)
10f	148–149	Yellow granules (petroleum benzin)	$C_{19}H_{12}N_2O_2$	75.99 (75.78)	4.03 (3.84)	9.33 (9.53)
10g	136.5–137.5	Slightly brown prisms (MeOH)	$C_{19}H_{12}N_2OS$	72.13 (71.87)	3.82 (3.84)	8.85 (8.76)
11d	144–145	Yellow needles (petroleum benzin)	$C_{13}H_{10}N_2O_2S$	60.45 (60.24)	3.90 (3.72)	10.85 (10.84)
13a	103–104	Yellow prisms (MeOH)	$C_{15}H_{10}N_2O$	76.91 (76.96)	4.30 (4.32)	11.96 (11.97)
13c	109–110	Yellow needles (petroleum benzin)	$C_{13}H_9N_2OCl$	67.05 (66.93)	3.38 (3.32)	10.43 (10.46)
13d	117–118	Yellow needles (petroleum benzin)	$C_{16}H_{12}N_2O$	77.40 (77.00)	4.87 (4.81)	11.28 (11.28)
13e	100.5–102	Yellow prisms (benzene-petroleum benzin)	$C_{16}H_{12}N_2O_2$	72.72 (72.25)	4.58 (4.51)	10.60 (10.58)
13f	160–161	Pale yellow needles (MeOH)	$C_{13}H_8N_2O_2$	69.64 (69.55)	3.60 (3.72)	12.49 (12.68)
13g	147	Yellow needles (MeOH)	$C_{13}H_8N_2OS$	64.98 (64.45)	3.36 (3.33)	11.66 (11.35)

Table 2. IR and ^{1}H-NMR Spectral Data for 2-Aroylquinoxalines (**5**, **6**), 1-Aroylphthalazines (**10**, **11**), and 4-Aroycinnolines (**13**).

Compd	IR (KBr) cm^{-1}	^{1}H-NMR ($CDCl_3$) δ (ppm)
5a	1660 (CO)	7.38-8.40 (9H, m, aromatic H), 9.53 (1H, s, C^3-H)
5c	1674 (CO)	7.44 (2H, d, J = 9 Hz, phenyl), 7.70-8.33 (6H, m, aromatic H), 9.42 (1H, s, C^3-H)
5e	1644 (CO)	6.92 (2H, d, J = 9 Hz, phenyl), 7.70-8.38 (6H, m, aromatic H), 9.36 (1H, s, C^3-H)
6a	1673 (CO)	7.22-8.36 (14H, m, aromatic H)
6b	1671 (CO)	7.20-8.37 (13H, m, aromatic H)
6c	1674 (CO)	7.18-8.35 (13H, m, aromatic H)
6d	1664 (CO)	2.42 (3H, s, Me), 7.13-8.40 (13H, m, aromatic H)
6e	1661 (CO)	3.85 (3H, s, OMe), 6.91 (2H, d, J = 9 Hz, aromatic H), 7.20-8.46 (11H, m, aromatic H)
6f	1660 (CO)	6.52-6.68 (1H, m, aromatic H), 7.27-8.40 (11H, m, aromatic H)
6g	1642 (CO)	7.06-8.37 (12H, m, aromatic H)
10a	1661 (CO)	7.46-8.43 (14H, m, aromatic H)
10b	1667 (CO)	7.50-8.49 (13H, m, aromatic H)
10c	1660 (CO)	7.34-8.41 (13H, m, aromatic H)
10d	1665 (CO)	2.43 (3H, s, Me), 7.28 (2H, d, J = 9 Hz, aromatic H), 7.49-8.37 (11H, m, aromatic H)
10e	1660 (CO)	3.90 (3H, s, OMe), 6.97 (2H, d, J = 9 Hz, aromatic H), 7.50-8.30 (11H, m, aromatic H)
10f	1638 (CO)	6.60 (1H, dd, J = 4, 2 Hz, furan), 7.47-8.30 (10H, m, aromatic H), 8.46-8.37 (1H, m, furan)
10g	1640 (CO)	7.10-8.80 (12H, m, aromatic H)
11d	1656 (CO)	2.42 (3H, s, Me), 3.09 (3H, s, Me), 7.26 (2H, d, J = 9 Hz, aromatic H), 7.77-8.30 (6H, m, aromatic H)
13a	1669 (CO)	7.27-8.04 (8H, m, aromatic H), 8.47-8.69 (1H, m, C^5-H), 9.20 (1H, s, C^3-H)
13c	1663 (CO)	7.30-7.97 (7H, m, aromatic H), 8.48-8.73 (1H, m, C^5-H), 9.19 (1H, s, C^3-H)
13d	1660 (CO)	2.46 (3H, s, Me), 7.24 (2H, d, J = 9 Hz, aromatic H), 7.54-8.06 (5H, m, aromatic H), 8.48-8.72 (1H, m, C^5-H), 9.22 (1H, s, C^3-H)
13e	1648 (CO)	3.86 (3H, s, OMe), 6.91 (2H, d, J = 9 Hz, aromatic H), 7.60-8.02 (5H, m, aromatic H), 8.46-8.72 (1H, m, C^5-H), 9.22 (1H, s, C^3-H)
13f	1643 (CO)	6.60 (1H, dd, J = 4, 2 Hz, furan), 7.19 (1H, d, J = 4 Hz, furan), 7.66-8.23 (4H, m, aromatic H), 8.47-8.69 (1H, m, C^5-H), 9.38 (1H, s, C^3-H)
13g	1635 (CO)	7.70-7.20 (1H, m, thiophene), 7.41-7.58 (1H, m, thiophene), 7.70-8.22 (4H, m, aromatic H), 8.52-8.77 (1H, m, C^5-H), 9.40 (1H, s, C^3-H)

These results are shown in Scheme 3.

Preparation of 1-Aroylphthalazines (10, 11) and 4-Aroylcinnolines (13). General Procedure

Sodium hydride (60% in oil, 144 mg, 3.6 mmol) was added to a solution of 1-chlorophthalazine (**8**, **9**, 3.0 mmol) or 4-chlorocinnoline (**12**, 3.0 mmol), 1,3-dimethylimidazolium iodide (**1a**, 224 mg 1.0 mmol), and sodium sulfinate [sodium methanesulfinate (**7a**): 102 mg (1.0 mmol) or sodium *p*-toluenesulfinate (**7b**): 178 mg (1.0 mmol)] in 20 mL of DMF and the mixture was stirred at 80 °C. The reaction mixture was poured into ice-H_2O, neutralized with AcOH, and extracted with AcOEt. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on SiO_2 with benzene then $CHCl_3$. The fraction eluted with $CHCl_3$ gave the ketone (**10**, **11** or **13**). These results are shown in Schemes 4 and 5. The spectral data for newly obtained ketones (**5**, **6**, **10**, **11**, **13**) are shown in Tables 1 and 2.

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