REACTION OF α-BROMOACETOPHENONE PHENYLSULFONYLHYDRAZONES. A NEW SYNTHETIC ROUTE TO 2-ARYLIMIDAZOISOQUINOLINES AND -QUINOLINES[1]

Suketaka Ito,* Akikazu Kakehi, and Toshikazu Miwa

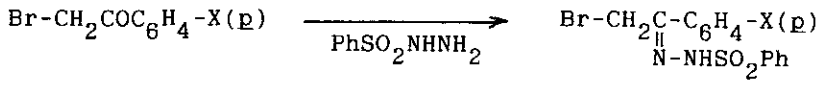
Department of Industrial Chemistry, Faculty of Engineering, Shinshu University, Wakasato, Nagano 380

Abstract — 2-Arylimidazo[2,1-a]isoquinolines and -[1,2-a]-quinolines were obtained in good to moderate yields by the reaction of the title hydrazones with isoquinoline and quinoline, respectively.

As has been seen in the Bamford-Stevens[2] and its related reactions,[3] arylsulfonylhydrazone derivatives are characterized by the elimination of arenesulfinic acid on treatment with a base and attractive from the synthetic and mechanistic point of view. Arylsulfonylhydrazones of α-haloketones, however, undergo the 1,4-elimination of hydrogen halide giving arylsulfonylazoenes[4] by the action of base and few is known of the chemistry of these compounds except being a precursor of an ene-diazonium salt.[5]

In the present paper, we wish to describe the reaction of α-bromoacetophenone phenylsulfonylhydrazones (1) with isoquinoline (2) and quinoline (3) as nucleophiles leading to respective 2-arylimidazoisoquinoline and -quinoline formations together with releasing benzenesulfonamide.

Phenylsulfonylhydrazones (1) were obtained in good yields by the reaction of α-bromoketones with phenylsulfonylhydrazine (Scheme 1, Table 1). The ir and nmr spectral data of 1 are shown in Table 2.



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1a: X=H 1d: X=Me
1b: X=Br 1e: X=Ph
1c: X=Cl

Scheme 1

Table 1. α-Bromoacetophenone Phenylsulfonylhydrazones (1)

Hydrazone	Yield %	mp[a] °C	Formula	Found(Calcd)/% C	H	N
1a	83	141 – 142	$C_{14}H_{13}N_2O_2SBr$	47.39	3.72	8.13
				(47.60	3.71	7.93)
1b	81	139 – 140	$C_{14}H_{12}N_2O_2SBr_2$	38.72	2.75	6.59
				(38.91	2.80	6.48)
1c	88	143 – 144	$C_{14}H_{12}N_2O_2SBrCl$	43.52	3.15	7.50
				(43.37	3.12	7.23)
1d	85	135 – 137	$C_{15}H_{15}N_2O_2SBr$	49.02	4.05	7.74
				(49.06	4.12	7.63)
1e	88	122 – 124	$C_{20}H_{17}N_2O_2SBr$	55.80	3.99	6.52
				(55.95	3.99	6.52)

a) Recrystallized from ethanol, uncorrected.

Table 2. Spectral Data of Hydrazones

Hydrazone	Ir(KBr, ν, cm^{-1}) NH	C=N	SO_2	Nmr($CDCl_3$, δ, ppm)[a] CH_2	Aromatic H	CH_3
1a	3196	1588	1345, 1163	4.43s	7.67 – 8.56m	
1b	3197	1593	1362, 1169	4.39s	7.33 – 8.61m	
1c	3215	1588	1349, 1165	4.35s	7.61 – 8.56m	
1d	3198	1609	1349, 1168	4.39s	7.49 – 8.56m	2.50s
1e	3202	1602	1351, 1162	4.44s	7.60 – 8.56m	

a) Abbreviations are as follows: s, singlet; m, multiplet.

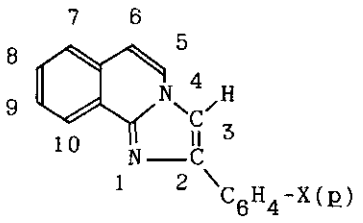
The reactions of 1 with 2 and with 3 were carried out throughout at room temperature. When an equimolar amount of 2 was added to a THF solution of 1, the separation of isoquinolinium salts was observed. Without isolation of the salts, the reaction mixtures were then stirred with an excess amount

of granular potassium carbonate (triple by the molar ratio to 1) for 2 - 3 day (Method A). Removal of inorganic substances from the reaction mixture and chromatographic treatment of residues gave 2-arylimidazo[2,1-a]isoquinolines (4) in good yields together with benzenesulfonamide and small quantities of unchanged 2 were also recovered. In the chromatographic treatment, the evolution of nitrogen was observed.[6] The results are summarized in Table 3. Isolation of isoquinolinium salts followed by treatment with the same amount of potassium carbonate as noted above in THF (Method B) gave analogous results, in which small amounts of isoquinoline were also recovered (Table 3). The reaction of 1 with 3 was conducted in a manner similar to that with 2: 2-arylimidazo[1,2-a]quinolines (5) were obtained in moderate yields along with benzenesulfonamide and unchanged 3 (Table 3). The reaction of 1 with pyridine gave the corresponding pyridinium salt, potassium carbonate treatmet of which resulted in no formation of 2-arylimidazopyridines, however. On the other hand, 2-aminopyridine reacted with 1 to give 2-arylimidazo[1,2-a]pyridines[7] together with the elimination of phenylsulfonylhydrazine.

The structure assignment of 4 and 5 was done on the basis of their analytical and spectral data, and the confirmation of known compounds was made also by direct comparison with authentic specimens. In the ir spectra, 4 and 5 exhibit a medium to weak peak at near 1630 cm^{-1} which can be assigned to a C=N streching mode. In addition, imidazoisoquinolines (4) have a characteristic strong absorption at near 1380 cm^{-1}; these 1630- and 1380-cm^{-1} absorptions have been also observed in imidazo[1,2-a]pyridines[8] and are in 2-arylimidazo[1,2-a]pyridines.[7] In contrast, imidazoquinolines (5) can be characterized by a medium peak at near 1330 cm^{-1} (Table 5): the absorption at near 1380 or 1330 cm^{-1} may be attributed to the ring vibration of imidazopyridine system.[9]

The present imidazoisoquinoline (or -quinoline) formation can be formulated by the cyclization of intermediate isoquinolinium (or quinolinium) 2-aryl-2-(phenylsulfonylhydrazono)ethylide followed by the elimination of benzenesulfonamide (Scheme 2).

Table 3. 2-Arylimidazo[2,1-a]isoquinolines (4) and -[1,2-a]-quinolines (5)



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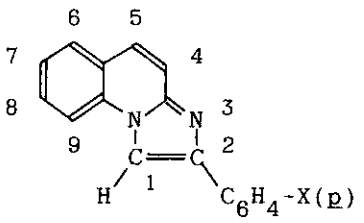


(5)

Compound	mp[a] °C	Yield/% A[b]	Yield/% B[c]	Recovered 2(3)/% A[b]	Recovered 2(3)/% B[c]
4a (X=H)	148 – 149[d]	64	70	20	15
4b (X=Br)	200 – 201[e]	84	89	8	7
4c (X=Cl)	192 – 193[f]	80	81	6	5
4d (X=Me)	159 – 160[g]	53	67	44	30
4e (X=Ph)	209 – 210[h]	72	54	7	5
5a (X=H)	117 – 118[i]	10	23	(80)	(65)
5b (X=Br)	203 – 204	52	56	(28)	(18)
5c (X=Cl)	199 – 201	32	43	(50)	(13)

a) Recrystallized from ethanol, uncorrected. b) Method A. c) Method B. d) Lit.,[12a] mp 145 – 148°C (MeOH); lit.,[12b] mp 148 – 150°C (MeOH). e) Lit.,[12b] mp 205 – 206°C (EtOAc). f) Lit.,[12b] 193 – 194°C (EtOAc). g) Lit.,[12b] mp 161 – 163°C (i-Pr_2O). h) Lit.,[12b] mp 221 – 222°C (methylenecellosolve). i) Lit.,[12a] mp 109 – 112°C (MeCN).

Table 4. Analytical data of Imidazoisoquinolines and -quinolines

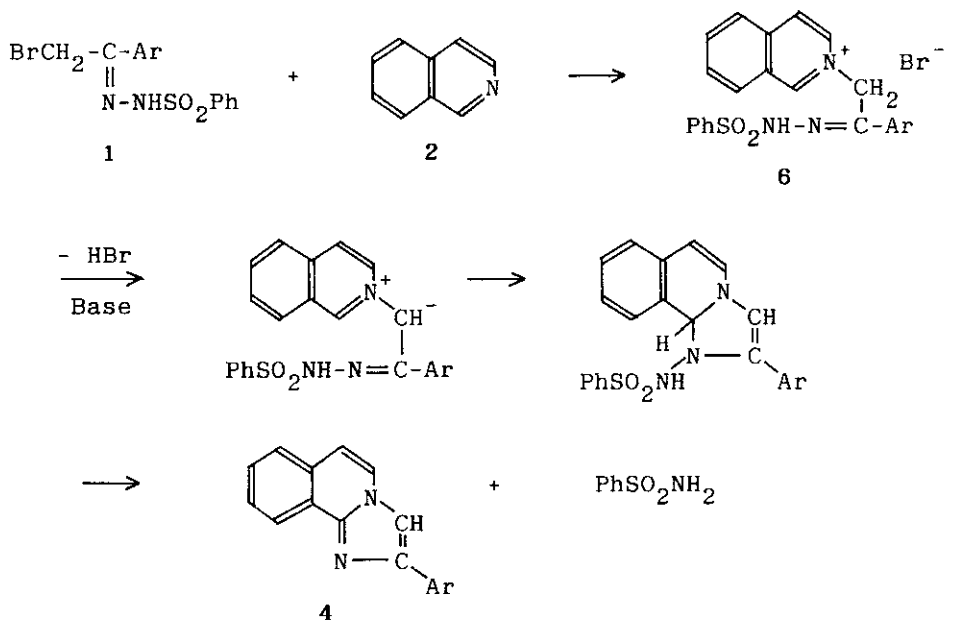
Compound	Formula	Calcd/% C	Calcd/% H	Calcd/% N	Found/% C	Found/% H	Found/% N
4a	$C_{17}H_{12}N_2$	83.58	4.95	11.47	83.52	4.92	11.56
4b	$C_{17}H_{11}N_2Br$	63.18	3.43	8.67	63.09	3.17	8.84
4c	$C_{17}H_{11}N_2Cl$	73.25	3.98	10.05	73.18	4.08	10.02
4d	$C_{18}H_{14}N_2$	83.69	5.46	10.84	83.74	5.47	11.01
4e	$C_{23}H_{16}N_2$	86.22	5.03	8.74	86.20	5.07	8.73
5a	$C_{17}H_{12}N_2$	83.58	4.95	11.47	83.35	4.83	11.54
5b	$C_{17}H_{11}N_2Br$	63.18	3.43	8.67	63.35	3.13	8.80
5c	$C_{17}H_{11}N_2Cl$	73.25	3.98	10.05	73.19	3.89	10.20

Table 5. Spectral Data of Imidazoisoquinolines and -quinolines

Compound	Ir(KBr, ν, cm^{-1})[a]		Nmr($CDCl_3$, δ, ppm)[b]			
	C=N	ring	3-CH(4)/1-CH(5)	10-CH(4)	Aromatic H	p-CH_3
4a	1635m	1382s	7.86s	8.60－8.90m	6.94－8.17m	
4b	1635m	1381s	7.90s	8.63－8.93m	7.00－8.10m	
4c	1635m	1380s	7.82s	8.67－8.93m	6.97－8.13m	
4d	1632m	1380s	7.82s	8.68－8.98m	6.91－8.11m	2.41s
4e	1631m	1380s	7.93s	8.70－9.00m	7.03－8.33m	
5a	1632w	1332m	8.28s		7.20－8.10m	
5b	1629w	1330m	8.38s		7.46－8.13m	
5c	1630m	1327m	8.32s		7.30－8.08m	

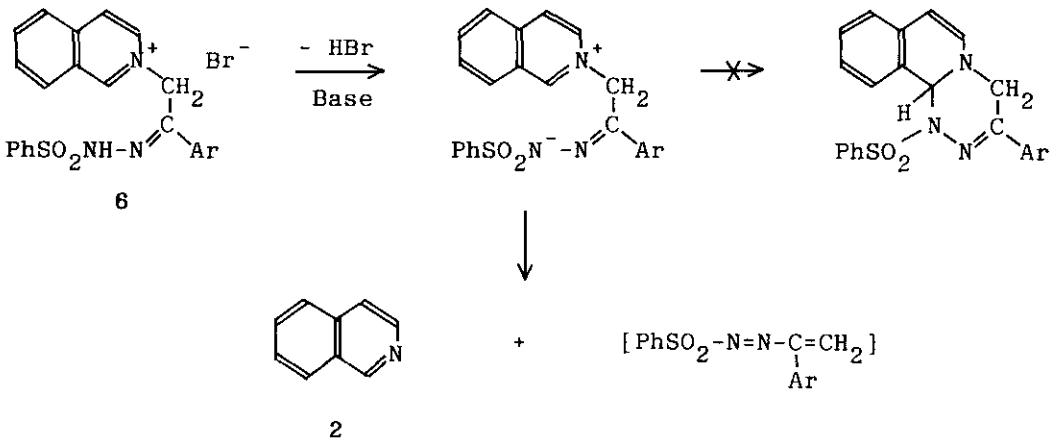
a) Abbreviations are as follows: m, medium; s, strong; w, weak.

b) Abbreviations are as follows: s, singlet; m, multiplet.



Scheme 2

In this reaction, the sulfonylamino group of isoquinolinium salt might function as a nucleophilic center to afford a triazine; however, this type of reaction was not observed. As shown in Table 3 (Method B), a certain amount of isoquinoline was recovered: the azoene formation by 1,4-elimination should proceed competitively (Scheme 3).



Scheme 3

When the 2-aryl group of hydrazonoethyl moiety bears an electron-donating substituent, the methylene-proton abstraction to form isoquinolinium ylide and its stability should be reduced; this substituent effect can be seen in the results (Table 3).

Frazer and Bradsher[10] have reported an unstable triazino[3,4-a]isoquinoline formation by the reaction of 2-phenacylisoquinolinium bromide with hydrazine hydrate. In this reaction, the hydrazono-amino group of intermediate 2-phenacylisoquinolinium bromide hydrazone acts as a nucleophilic center. Arenesulfonamido group is a good leaving group as seen in the diazo transfer reaction;[11] thus, 2-phenacylisoquinolinium bromide phenylsulfonylhydrazones (6) give stable aromatic imidazoisoquinolines with ease.

2-Arylimidazo[2,1-a]isoquinolines can be obtained by the reaction of 1-aminoisoquinoline with phenacyl bromides[12] and 2-arylimidazo[1,2-a]quinolines (or -[2,1-a]isoquinolines) by that of phenacylquinolinium (or -isoquinolinium) bromides with hydroxylamine hydrochloride, respectively.[12a] Since the latter reaction proceeds in an acidic medium, it should not be isoelectronic with the present reaction.

EXPERIMENTAL

Melting points were determined with a Yanagimoto MP-S3 micromelting point apparatus, and are uncorrected. The microanalysis was performed on a Perkin-Elmer 240 elemental analyzer. The ir and nmr spectra were recorded with a Hitachi 260-10 spectrophotometer and a Varian EM-360A spectrometer, respectively.

Preparation of α-Bromoacetophenone Phenylsulfonylhydrazones (1). General Procedure: A mixture of α-bromoacetophenone (50 mmol) and phenylsulfonylhydrazine (50 mmol) was dissolved in THF (50 ml) by heating (60°C, 15 min). Completion of reaction was checked by tlc and the resulting reaction mixture was allowed to cool overnight. After removal of small amounts of insoluble matter by filtration, the solution was concentrated, and then a 30-ml portion of benzene was added to the concentrate. The separated crystalline product was filtered and washed with benzene. The results are summarized in Table 1. The products were in a fairly pure state and used for the subsequent reactions; further purified products could be obtained by recrystallization from ethanol.

General Procedure for the Reaction of 1 with Isoquinoline (2). Method A: A solution of 2 (5 mmol) in THF (10 ml) was added to a solution of 1 (5 mmol) in THF (20 ml) by portions with stirring at room temperature. Without separation of isoquinolinium salts formed, granules of potassium carbonate were added to the reaction mixture, which was stirred for 2–3 days magnetically. After removal of inorganic substances by filtration, the reaction mixture was freed of solvent under reduced pressure. The resulting residue was chromatographed on a silica gel column (2.0 × 15 cm, eluent: benzene, benzene ether, and benzene ethanol systems) to give **4** (Table 3), along with unaltered 2 and benzenesulfonamide (mp 153–155°C; yield: 58%, in the reaction of p-bromoacetophenone derivative). **Method B:** The isoquinolinium salts formed in the first step were separated by filtration, dispersed in THF, and then treated in the same manner as above.

Reaction of 1 with Quinoline (3). Reactions were conducted in a similar manner as described above. The results are summarized in Table 3.

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7. 2-Phenylimidazo[1,2-a]pyridine: yield, 63%; mp 137 - 139°C; ir (KBr, cm^{-1}), 1638m, 1379s. 2-(p-Bromophenyl)imidazo[1,2-a]pyridine: 61%; 210 212°C; 1638m, 1375s. 2-(p-Chlorophenyl)imidazo[1,2-a]pyridine: 60%; 207 208°C; 1638m, 1379s.
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Received, 12th August, 1991