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A Facile Synthesis of Sulfides Using S-Aryl-isothiuronium Intermediates

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A variety of sulfides were conveniently prepared by a treatment of aryl iodides with thiourea in the presence of a nickel(0) catalyst, then with CaO, and finally with a variety of electrophiles such as alkyl, acyl, silyl, aryl, or alkenyl halides.

A synthetic procedure of organosulfur compounds (RSB; B=H, alkyl etc.) from the corresponding halides (RX) has been investigated extensively.$^{1)}$ An application of S-aryl-isothiuronium salts (2) to such transformation seems attractive, since (i) 2 is now readily available from aryl halides (1)$^{2)}$ and (ii) a transformation of 2 to ArSB-type compounds (4) is conceivable.

$$\underset{1}{\mathrm{ArX}} \xrightarrow[\mathrm{Ni(0)}]{(\mathrm{H_2N})_2\mathrm{C{=}S}} \underset{2}{\mathrm{Ar\overset{+}{S}{-}C(NH_2)_2\ X^-}} \xrightarrow{\text{Base}} \underset{3}{\mathrm{ArS^-}} \xrightarrow[(\mathrm{Ni(0)})]{\mathrm{B^+}} \underset{4}{\mathrm{ArS{-}B}}$$

It is well-known that a treatment with alkali effects an efficient hydrolysis of 2 to the corresponding arenethiolates (3) readily.$^{3)}$ However, for our intended "one-pot" procedure (1 → 4), alkaline hydrolysis is unsuitable, since aqueous alkali might consume electrophiles (B^+), cause a heterogeneous system, and deactivate a nickel(0) species (vide infra) at the subsequent stage.

Then, a series of investigations were undertaken to find a profitable nonaqueous reagent for the transformation of 2 to 3. The results of the reaction between an appropriate base and in-situ generated 2 or the solution of S-aryl-isothiuronium tetraphenylborate$^{2)}$ followed by a quenching with HCl are listed in Table 1 (Runs 1-7). CaO induced the decomposition most effectively under mild conditions.$^{4)}$ Moreover, an excess of CaO did not disturb the proceeding of a nucleophilic displacement of alkyl halides with the resulting 3. Thus, a sequential transformation of 1 to 4 (B=alkyl) was achieved in one pot; a treatment of 1 with thiourea in the presence of a nickel(0) catalyst, then with CaO, and finally with alkyl halides afforded alkyl sulfides in good yields (Runs 8-10). A similar sequence using acyl halides or chlorosilanes in place of alkyl halides gave S-aryl thioesters or arylthiosilanes, respectively (Runs 11 and 12).

It is to be noted that in the presence of a nickel(0) catalyst, generated in situ from bis(triethylphosphine)nickel(II) chloride and sodium cyanoborohydride as a reducing agent, otherwise inert aryl halides reacted readily with thiolate anions to yield the corresponding sulfides in good yields.$^{5)}$ Since CaO did not deactivate the nickel(0) species, the transformation of 1 to 4 (B=aryl) was successfully performed in one pot, too (Runs 13-15). In the same way, a sequential treatment using alkenyl

Table 1. Synthesis of sulfides via a base-induced decomposition of S-phenyl-isothiuronium salts, followed by a reaction with electrophiles[a)]

Run	Base	Electrophile			B—SC_6H_5
		B—X	Temp	Time	Yield[b)]
			θ_m/°C	h	%
1	CaO	H—Cl	25	-	52
2	NaH	H—Cl	25	-	43
3	KO^tBu	H—Cl	25	-	38
4	K_2CO_3	H—Cl	25	-	23
5	NEt_3	H—Cl	25	-	10
6	Cu_2O	H—Cl	25	-	<1
7[c)]	CaO	H—Cl	25	-	62
8	CaO	CH_3—I	25	3	100
9	CaO	$C_{10}H_{21}$—Br	25	7	97
10	CaO	CH_3OCH_2—Cl	25	0.5	(90)
11	CaO	CH_3CO—Cl	25	0.1	100
12	CaO	$(CH_3)_3Si$—Cl	25	0.3	80
13	CaO	C_6H_5—I	60	20	97
14	CaO	C_6H_5—I[d)]	60	4	(95)
15	CaO	C_6H_5—I[d)]	40	40	94
16	CaO	(*E*)-C_6H_5CH=CH—Br[d)]	60	8	(95)[e)]
17	CaO	(*Z*)-C_6H_5CH=CH—Br[d)]	60	20	(90)[f)]

a) Molar ratio of each reagent (2/Base/B—X) was 1/1.5-2/1.1-1.5. The base-induced decomposition of 2 was carried out at 25 °C for 0.5 h (Runs 1-6), 1 h (Run 7), or 1.5 h (Runs 8-17). In Runs 1-7, resulting benzenethiolate was quenched with 2 mol dm^{-3} HCl.

b) Yields were determined by GLC. Yields in parentheses were isolated ones.

c) DMF solution of S-phenyl-isothiuronium tetraphenylborate was used.

d) Both $(PEt_3)_2NiCl_2$ and $NaBH_3CN$ were added together with electrophiles.

e) *E*/*Z*=100/0.

f) *E*/*Z*=10/90.

halides instead of aryl halides gave 4 (B=alkenyl) in a stereospecific manner (Runs 16 and 17).[6)]

Thus, the present method enables a facile synthesis of a variety of sulfides from not ill-smelling thiols but easily handling aryl halides, which expands the utility of readily available S-aryl-isothiuronium salts in organic synthesis.

References

1) See for example, M. R. Bowman, H. Heaney, and P. G. Smith, Tetrahedron Lett., 25, 5821 (1984); P. Molina, M. Alajarin, M. J. Vilaplana, and A. R. Katritzky, ibid., 26, 469 (1985); S. Fujisaki, I. Fujiwara, Y. Norisue, and S. Kajigaeshi, Bull. Chem. Soc. Jpn., 58, 2429 (1985).

2) K. Takagi, Chem. Lett., 1985, 1307; 1986, 265.

3) R. F. Pratt and T. C. Bruice, J. Am. Chem. Soc., 94, 2823 (1972).

4) The exact mechanism is not clear as yet. However, the fact that NH_2CN was detected in the reaction mixture suggests that the reaction path is similar to that operated in alkaline hydrolysis.[3)]

5) Pd(0)- or Ni(II)-catalyzed nucleophilic displacement of alkenyl halides or aryl halides with thiolate anions was recently reported: S. Murahashi, M. Yamamura, K. Yanagisawa, N. Mita, and K. Kondo, J. Org. Chem., 44, 2408 (1979); T. Migita, T. Shimizu, Y. Asami, J. Shiobara, Y. Kato, and M. Kosugi, Bull. Chem. Soc. Jpn., 53, 1385 (1980); H. J. Cristau, B. Chabaud, R. Labaudiniere, and H. Christol, Organometallics, 4, 657 (1985); idem, J. Org. Chem., 51, 875 (1986).

6) Typical example is as follows: Crushed CaO (3 mmol) and DMF (2.5 mL) was added to a DMF solution of S-(4-methoxycarbonylphenyl)-isothiuronium iodide, which was preformed by a stirring of a mixture of methyl 4-iodobenzoate (2 mmol), thiourea (3 mmol), $(PEt_3)_2NiCl_2$ (0.04 mmol), $NaBH_3CN$ (0.06 mmol), and DMF (1 mL) at 60 °C for 4 h. After 1.5 h of stirring at 25 °C, iodobenzene (2.2 mmol), $(Et_3P)_2NiCl_2$ (0.04 mmol), and $NaBH_3CN$ (0.06 mmol) was added and stirring was continued for 4 h at 60 °C under nitrogen. The resultant mixture was chromatographed on a silica-gel column using hexane-ethyl acetate as the eluant. 438 mg of methyl 4-(phenylthio)benzoate was obtained(90%). Mp 76-77 °C (lit.,[7)] 75-76 °C).

7) L. Benati, C. M. Camaggi, and G. Zanardi, J. Chem. Soc., Perkin 1, 1972, 2817.

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