BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 52 (11), 3461—3462 (1979)

A Catalytic Effect of Amines on the Reaction of α-Toluenethiol with N,N'-Thiodiphthalimide[1)]

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(Received March 5, 1979)

Synopsis. In the presence of catalytic amounts of several amines, *N,N'*-thiodiphthalimide has been allowed to react with α-toluenethiol in benzene and dichloromethane giving *N*-(benzyldithio)phthalimide. *N*-(Benzyldithio)phthalimide has been obtained in excellent yields with 2,4- or 2,6-lutidine as the catalyst in benzene.

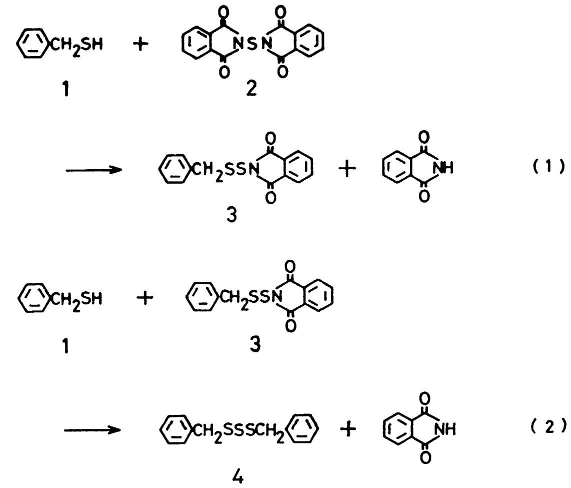
Harpp *et al.*[2)] prepared the *N*-(alkyldithio)- and *N*-(aryldithio)phthalimides in good yields by the reaction of thiols with *N,N'*-thiodiphthalimide(**2**) in refluxing benzene. In a previous paper,[3)] it was shown that a catalytic amount of imidazole markedly accelerates Harpp's reaction in dichloromethane. This has lead to the present examination as to whether amines act as catalysts in the present reaction.

A mixture of α-toluenethiol (**1**) (5 mmol), **2** (5 mmol), and amine (0.5 mmol) was refluxed for 30 min in benzene (100 ml). The starting material **2** was not sufficiently soluble in hot benzene, but the product, *N*-(benzyldithio)phthalimide (**3**), and phthalimide were soluble. Consequently, the dissolution of **2** promotes the reaction. The product **3** was isolated from the reaction mixture by fractional dissolution in cold benzene and cold ethanol, and weighed. The remaining reaction mixture was subjected to column chromatography. The eluate obtained gave a mixture of the unchanged thiol and a by-product, dibenzyl trisulfide (**4**), which were identified and evaluated from NMR analysis,[4)] the results of which are summarized in Table 1. As shown in the material balance of the benzyl group in Table 1, the compounds stemming from **1** collected exceeded 90% with few exceptions.

The unchanged thiol (93%) was recovered in the absence of amine in the reaction mixture (Run 1). Regardless of the functional group, *i.e.*, primary, secondary, or tertiary, all amines accelerated the present reaction. The product distribution varied with the amine employed, the results of which are given in Table 1. The results can be classified into three categories: (1) the thiol remaining practically unchanged (Runs 1—5); (2) the thiol being quantitatively changed into **3** (Runs 6—10); (3) the thiol being consumed to give mainly **3** but the remaining (over 20%) was changed into **4** (Runs 11—16). The variety in product distribution appears directly related to the pK_a value of the amine used. With the amine having a pK_a value of 5.06 or less, the unchanged thiol was recovered in over 25% of the initially charged amount. When 2,6- or 2,4-lutidine having a pK_a value of 6.75 or 6.79, respectively, was applied to the reaction system, **3** was obtained almost quantitatively. A pK_a value of 6.95 or greater caused a decrease in the yield of **3**. The yield of **4** increased with an increase in the pK_a value of the amine.[5)]

Recently, Yamabe *et al.*[6)] reported that 1 : 1 S–H–N type hydrogen bonding is formed between 1-propanethiol and several amines, and that the strength of the hydrogen bonding enhances with increase in the pK_a value of the amine. Therefore, the present reaction is expected to proceed rapidly to give **3** in a good yield since the nucleophilicity of the thiol toward **2** would increase in the presence of a strongly basic amine.

Table 1 shows that, in spite of the reaction of **2** with one equivalent of **1**, an undesirable trisulfide **4** was produced. This suggests that the thiol reacted competitively with the starting material **2** and product **3** (Eqs. 1 and 2). The thiol predominantly reacted with **2** to give **3** when the nucleophilicity was suitable; this corresponds to a pK_a value of the amine of approximately 6.7 (Runs 7 and 8). As the nucleophilicity of the thiol increases, the two reactions occur giving both **3** and **4**. A second interpretation in formation of **4** is as follows. The starting material **2** does not dissolve adequately in hot benzene, and consequently the reaction rate of the thiol having a large nucleophilicity toward **2** may be limited by the rate of solution **2** into the benzene, and thus the reaction with **3** will increase giving **4**. The formation of **4** in the case of weak amines (Runs 2—6) is impossible to explain completely by the above reaction mechanisms. Amines having large pK_a values abstract protons from arylalkyl hydrodisulfide but amines having small pK_a values attack the sulfur atoms of the compound.[7)] There is a possibility in the present reaction that the amine having a small pK_a value attacks the electron-deficient sulfur atom of **2** and **3** as a nucleophile but the actual reaction mechanism remains obscure.[8)]



In order to increase the yield of **3** but to decrease that of **4**, a mixture of **1** and **2** was refluxed for 20

TABLE 1. REACTIONS OF **1** WITH **2** IN THE PRESENCE OF AMINES[a]

Run	Amine	$\mathrm{p}K_\mathrm{a}$	Solvent	Recovered **1** (mmol)	Products		Material Balance of benzyl group[c]
					3 (mmol)[b]	**4** (mmol)	
1	None	—	Benzene	4.65	0.12 (3)	0	4.89
2	Aniline	4.60	Benzene	3.01	1.09 (22)	0.32	4.74
3	2-Aminophenol[d]	4.72	Benzene	2.04	2.38 (48)	0.09	4.60
4	*N*-Methylaniline	4.85	Benzene	2.48	0.79 (16)	0.43[e]	4.13
5	*N*,*N*-Dimethylaniline	5.06	Benzene	1.08	1.55 (31)	0.49	3.61
6	Pyridine	5.17	Benzene	Trace	3.44 (69)	0.68[f]	4.80
7	2,6-Lutidine	6.75	Benzene	0	4.84 (97)	0.08	5.00
8	2,4-Lutidine	6.79	Benzene	0	4.82 (96)	0.09	5.00
9	Imidazole	6.95	Benzene	0	4.45 (89)	0.31[e]	5.07
10	*N*-Methylmorpholine	7.41	Benzene	0	4.47 (89)	0.20	4.87
11	Morpholine	8.36	Benzene	0	3.92 (78)	0.50	4.92
12	Butylamine	10.60	Benzene	0	3.20 (64)	0.90	5.00
13	Triethylamine	10.67	Benzene	0	1.98 (40)	1.52	5.01
14	Tributylamine	10.87	Benzene	0	2.70 (54)	1.15	5.00
15	Piperidine	11.22	Benzene	0	0.82 (16)	2.02	4.86
16	Dibutylamine	11.25	Benzene	0	2.14 (43)	1.39	4.93
17	None	—	Dichloromethane	3.60	0.44 (9)	0	4.04
18	Aniline	4.60	Dichloromethane	0	4.43 (89)	0.08	4.61
19	Imidazole	6.95	Dichloromethane	0	4.26 (85)	0.17	4.60
20	Triethylamine	10.67	Dichloromethane	0	3.60 (72)	0.70	5.00
21	Piperidine	11.22	Dichloromethane	0	2.96 (59)	0.81	4.58

a) All the reactions were performed by the use of **1** (5 mmol), **2** (5 mmol), amine (0.5 mmol) in a solvent (100 ml) at boiling point for 30 min in benzene and 20 min in dichloromethane. b) Values in parentheses show the yield based on **2** used. c) Summation of mmol of recovered **1** and **3** and two-fold mmol of **4**. The Theoretical value is 5.00. d) The $\mathrm{p}K_\mathrm{a}$ value of phenol group is 9.71. e) The product unidentified was detected other than listed. f) The value includes dibenzyl polysulfide besides trisulfide.

min in dichloromethane which is able to dissolve **2** completely. It is expected that the nucleophilicity of the thiol in polar solvents increases because the hydrogen bonding between thiol and amine is enhanced by the polar solvent.[6] As seen in Run 17 of Table 1, the reaction without amine proceeded hardly as in benzene. Even with amines possesing small $\mathrm{p}K_\mathrm{a}$ values, the reaction was significantly accelerated and gave **3** in good yield (Run 18). The formation of the by-product **4** was not sufficiently depressed by use of this reaction system.

References

1) Chemistry of *N*-(Organothio)imides. VI. For part V of this series, see Y. Abe, K. Oka, R. Kiritani, R. Akaki, and T. Fukumoto, *Ann. Rep. Rad. Ctr. Osaka*, **18**, 77 (1977).

2) D. N. Harpp and D. K. Ash, *Int. J. Sulfur Chem.*, *A*, **1**, 57 (1971).

3) Y. Abe and K. Oka, *Ann. Rep. Rad. Ctr. Osaka*, **18**, 75 (1977).

4) S. Kawamura, T. Kitao, T. Nakabayashi, T. Horii, and J. Tsurugi, *J. Org. Chem.*, **33**, 1179 (1968).

5) In the cases of triethylamine and piperidine, **4** was isolated in better yield than that expected from the respective $\mathrm{p}K_\mathrm{a}$ values. A possible explanation is that the $\mathrm{p}K_\mathrm{a}$ value of the amines cited in Table 1 were determined in aqueous solution whereas the present reaction was conducted in benzene.

6) T. Yamabe, K. Akagi, T. Hashimoto, S. Nagata, and K. Fukui, *J. Chem. Soc., Faraday Trans. 1*, **73**, 1860 (1977).

7) J. Tsurugi, Y. Abe, T. Nakabayashi, S. Kawamura, T. Kitao, and M. Niwa, *J. Org. Chem.*, **35**, 3263 (1970).

8) It has been known that the reaction of **2** with one equivalent of secondary amines gives *N*-(secondary aminothio)-phthalimides, and with two equivalent of those affords *N*,*N*′-thiodiamines. D. N. Harpp and T. G. Back, *Tetrahedron Lett.*, **1972**, 1481.