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ELEMENTAL SULFUR-CATALYZED SYNTHESIS OF N,N'-DISUBSTITUTED 1,3-DIIMINOISOINDOLINES FROM PHTHALONITRILE WITH AMMONIA AND AMINES

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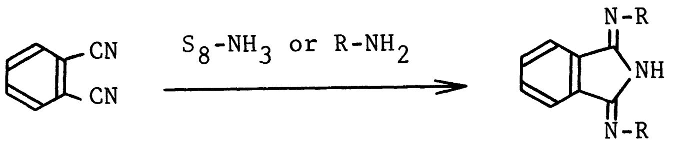
Various N,N'-disubstituted 1,3-diiminoisoindolines were synthesized by the elemental sulfur-catalyzed reaction of phthalonitrile with ammonia and some primary amines in excellent yields. Several functionalized isoindolines were also obtained in high yields.

Recently, we have developed some new reactions of organic compounds with elemental sulfur in liquid ammonia and amines. The previous our studies revealed that elemental sulfur in liquid ammonia and amines behaved as nucleophile,1) reductant,2) and oxidant3) in the reactions with many organic compounds. Thus, elemental sulfur has become a versatile reagent for synthetic organic chemistry. In order to establish further utility of elemental sulfur in liquid ammonia and amines, our interests focused on catalytic reaction with elemental sulfur. We have now found a new reaction catalyzed by elemental sulfur producing N,N'-disubstituted 1,3-diiminoisoindolines(2) from phthalonitrile(1) with ammonia and amines in excellent yields. For the preparation of 1,3-diiminoisoindolines, there is only a few report, that is, the reaction of phthalonitrile with methanol-ammonia at high temperature,4) with sodium amide in formamide5) and with sodium methoxide-ammonia in methanol.6) In this communication, we wish to report preliminarily the new method for preparation of N,N'-disubstituted 1,3-diiminoisoindolines, which is catalyzed by elemental sulfur in liquid ammonia and amines, as shown in Eq.1.

Typical procedure is as follows. Liquid ammonia or primary amine(10 ml) was charged into a titanium autoclave or flask containing phthalonitrile(1)



(1)

1 2a-j

(1.0 mmol) and elemental sulfur(0.5 mg atom). The solution was allowed to react with stirring by magnetic stirrer. After completion of the reaction, the ammonia or amine was removed by evaporation. The reaction mixture obtained by usual work up was chromatographed on silica-gel(WAKO Gel C-300) using chloroform/methanol(1/5) as eluent to give N,N'-disubstituted 1,3-diiminoisoindoline(2) along with only trace of unreacted phthalonitrile(1) and elemental sulfur. These results are summarized in Table 1. The obtained products, 1,3-diiminoisoindoline(2), were identified by comparing the NMR, IR, MS, and elemental analysis with those of authentic samples.

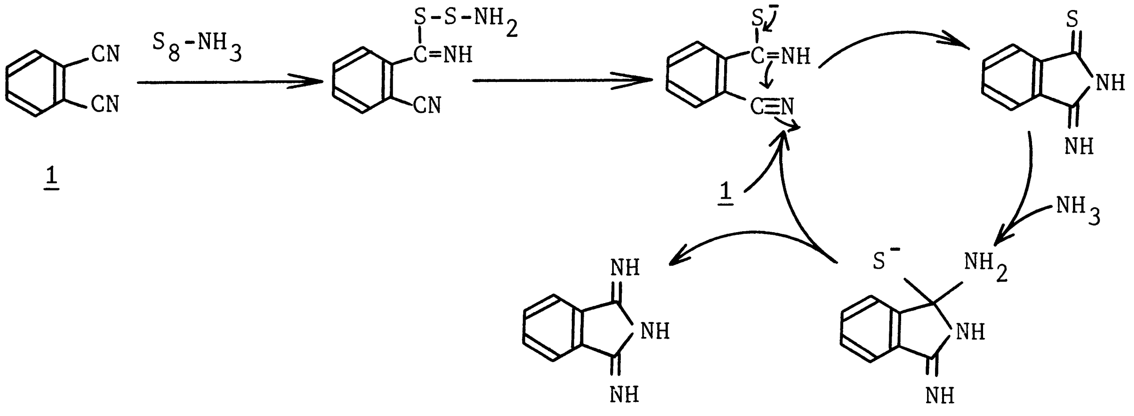
As shown in Table 1, various N,N'-disubstituted 1,3-diiminoisoindolines (2a-j) were obtained in high yields. That functionalized 1,3-diiminoisoindolines(2f-h) bearing hydroxyl group in the molecule were also obtained by the reactions of substrate(1) with 2-hydroxyethyl-, 3-hydroxypropyl-, and 5-hydroxypentylamines in the presence of elemental sulfur(runs 13, 14,and 15) suggested a possibility of further application of such isoindolines to new heterocyclic systems. Secondary and tertiary amines did not react essentially with phthalonitrile(1), even in the presence of elemental sulfur.

It should be noted that no reaction was observed in the absence of elemental sulfur(run 5), whereas 1,3-diiminoisoindoline(2a) was obtained sufficiently in the presence of only 0.3 equiv. of elemental sulfur(run 3). In contrast to the known reaction of (1) with methanol-methylamine by which isoindoline(2b) was obtained in only 74% yield at 100 °C,$^{4)}$ present reaction in the presence of elemental sulfur provided a facile formation of isoindoline(2b) in quantitative yield even at 40 °C(run 9). Moreover, we examined the catalytic effect of thiolate anion such as benzenethiolate or sodium hydrosulfide instead of elemental sulfur, showing that desired isoindoline was not at all or only insufficiently obtained as shown in Table 1(runs 6 and 7). These facts clearly show that elemental sulfur has an inherent catalytic effect for this reaction.

Table 1. Synthesis of N,N'-Disubstituted 1,3-Diiminoisoindolines from Phthalonitrile with Ammonia or Amines in the Presence of Elemental Sulfur

Run	Amine	React. Cond.		Catalyst	Yield of product	
	$R-NH_2/R$	Temp/°C	Time/h	S_8/mg atom	Isoindoline(2)/%$^{a)}$	
1	H	100	3	1	65	2a
2	H	100	3	0.5	62	2a
3	H	100	3	0.3	60	2a
4	H	100	3	0.1	9	2a
5	H	100	3	0	no reaction	
6	H	100	3	$1^{b)}$	no reaction	
7	H	100	3	$1^{c)}$	34	2a
8	H	100	6	1	100	2a
9	CH_3-	40	3	1	99	2b
10	$CH_3CH_2CH_2$-	$49^{d)}$	2	1	96	2c
11	$CH_3CH_2CH_2CH_2$-	60	1	1	94	2d
12	Cyclohexyl	60	1	1	94	2e
13	$HO-CH_2CH_2$-	60	1	1	87	2f
14	$HO-CH_2CH_2CH_2$-	60	1	1	89	2g
15	$HO-CH_2CH_2CH_2CH_2CH_2$-	60	1	1	86	2h
16	$Ph-CH_2$-	40	1	1	98	2i
17	$Ph-CH_2CH_2$-	40	4	1	86	2j

a) Isolated yield based on the phthalonitrile. b) Benzenethiol was used as a catalyst. c) As a catalyst sodium hydrosulfide was served. d) The reaction was carried out under refluxing propylamine.



Scheme 1. 2

Although at present stage any intermediates could not be detected, a plausible pathway involving a nucleophilic attack of aminothiolate on cyano group followed by cyclization to isoindoline is depicted in Scheme 1 based on the reactivity of the aminothiolate from elemental sulfur in liquid ammonia$^{7)}$ and the catalytic effect mentioned above. As it is well known that 1,3-diiminoisoindoline is an important intermediate for the preparation of porphyrines,$^{8)}$ and phthalocyanines,$^{9)}$ therefore, the present reaction must be to provide very useful procedure for synthetic organic and bioorganic chemistry. Further investigations on the mechanism and the application of this reaction are now in progress.

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