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SYNTHESIS OF 1,3-DIIMINOISOINDOLINES FROM 2-CYANOBENZALDEHYDE. REACTION OF N-(2-CYANOBENZYLIDENE)ANILINES WITH ELEMENTAL SULFUR IN LIQUID AMMONIA AND AMINES

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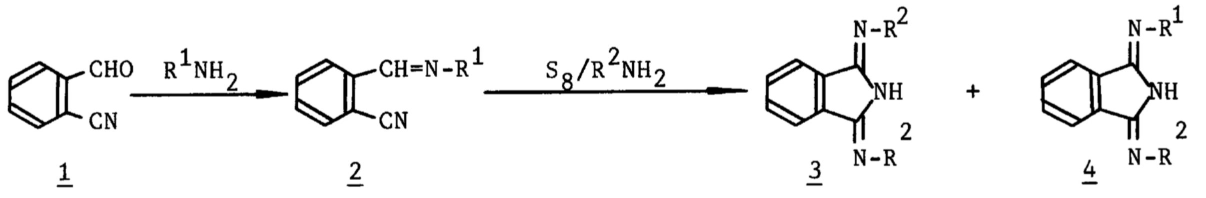
Various 1,3-diimonoisoindolines were obtained by treating N-(2-cyanobenzylidene)anilines with elemental sulfur in liquid ammonia and amines. A novel route to isoindoline from 2-cyanobenzaldehyde was developed.

It is well known that isoindoline is an important intermediate for preparation of porphyrines[1)] and phthalocyanines.[2)] There are, however, only a few reports on the method for preparation of isoindolines, e.g., the reaction of phthalonitrile with methanol-ammonia at high temperature,[3)] with sodium amide in formamide[4)] and with sodium methoxide-ammonia in methanol.[5)] Recently, we have reported the reaction of phthalonitrile with elemental sulfur in liquid ammonia and amines affording 1,3-(N,N'-dialkyl)-1,3-diiminoisoindolines quantitatively and revealed that this reaction is a new type of elemental sulfur catalyzed reaction.[6)] On the other hand, we have successfully obtained 3-alkylaminoisoindolenones by treating 2-cyanobenzaldehyde with primary and secondary alkylamines at room temperature in excellent yields.[7)] In this reaction, aromatic amines such as aniline gave Schiff base, N-(2-cyanobenzylidene)aniline, in preference to isoindolenone. In connection with the various reactivities of elemental sulfur in liquid ammonia,[6,8)] the above two reactions stimulated us to explore a new synthesis of isoindoline from 2-cyanobenzaldehyde via N-(2-cyanobenzylidene)aniline with elemental sulfur in liquid ammonia and amines. We wish to report on elemental sulfur induced cyclization of N-(2-cyanobenzylidene)aniline(2) giving symmetrical(3) and unsymmetrical isoindolines

(4)(Scheme 1).

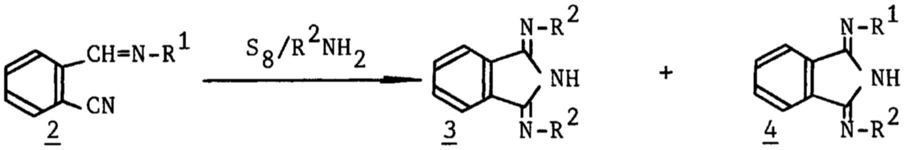


Scheme 1.

Typical procedure is as follows. N-(2-Cyanobenzylidene)-4-mehtoxyaniline (2)(0.5 mmol), which was readily prepared by the reaction of 2-cyanobenzaldehyde (1) with 4-methoxyaniline, and elemental sulfur(1 mg atom) were taken into a titanium autoclave. After evacuation, liquid ammonia(10 ml) was charged into the autoclave and then the mixture was allowed to react at 60 °C for 3 h. Desired 1,3-diiminoisoindoline(3) and 1-[N-(4-methoxyphenyl)]-1,3-diiminoisoindoline(4) were obtained after usual work up and subsequent column chromatography on silica gel using chloroform as eluent. The obtained 1-[N-(4-methoxyphenyl)]-1,3-diiminoisoindoline was characterized as follows. Mp 170 °C (dec.); ^{1}H-NMR ($CDCl_3$) δ = 8.05-6.62(m, 12H) and 3.76(s, 3H); IR(KBr): 3000 (≥NH) and 1650 cm^{-1} (C=N).9) The results are summarized in Table 1.

Various isoindolines were obtained in good total yields as shown in Table 1. When liquid ammonia was used, unsymmetrical isoindolines, 1-(N-aryl)-1,3-diiminoisoindoline(4), were preferentially obtained(runs 1,2,7,8, and 9). Especially, in the reaction of N-(2-cyanobenzylidene)-4-methoxyaniline, exclusive formation of 1-[N-(4-methoxyphenyl)]-1,3-diiminoisoindoline was observed in the ratio of 26:74(run 9). Introduction of electron-withdrawing groups such as 4-chloro or 3-chloro into the aromatic ring decreased the unsymmetrical 4 and increased the symmetrical isoindoline 3 (runs 10 and 11). It is noted that the reaction is not occurred in the absence of elemental sulfur even at 60 °C(run 5). This fact suggests that the elemental sulfur in liquid ammonia has played an important role in this reaction. In order to extend a generality of this method, alkylamines such as methyl-, propyl- and butylamines were employed. In contrast to the result in liquid ammonia, use of alkylamine gave predominantly symmetrical isoindoline, 1,3-(N,N'-dialkyl)-1,3-diiminoisoindoline(3)(runs 13-16). It is, however, noteworthy that 1-[N-(4-methylphenyl)]-3-(N-methyl)-1,3-diiminoisoindoline was the sole product when methylamine was used at 0 °C(run 17). Although secondary and tertiary amines can not give essentially any isoindolines(3 or 4), we have obtained an interesting product containing sulfur

Table 1. Synthesis of isoindolines from N-(2-cyanobenzylidene)anilines(2)

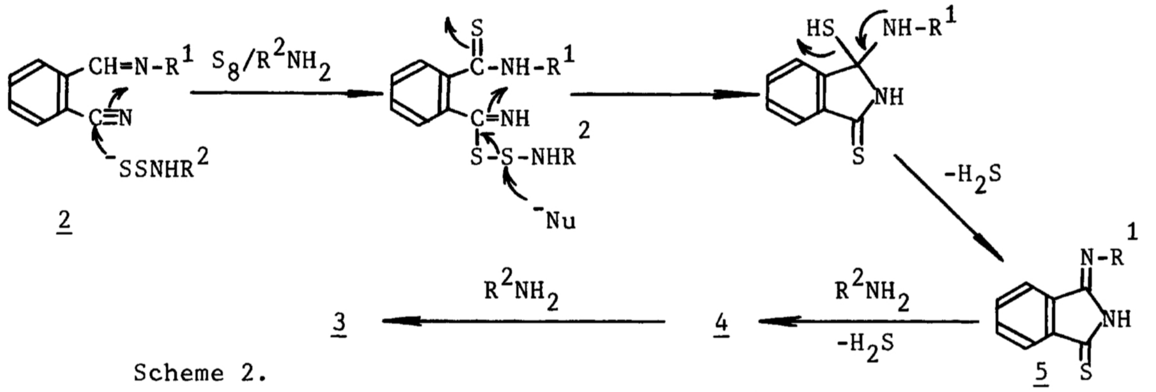


Run	Substituent R^1	Amine R^2	React. Temp /°C	React. Time/h	S_8 mg atom	Yield of 3+4/%[a)]	Ratio/3:4
1	$4\text{-}CH_3\text{-}C_6H_4$	H	60	3	1	57	25:75
2	"	H	60	3	2	77	43:57
3	"	H	60	6	1	59	46:54
4	"	H	60	1	1	28	50:50
5	"	H	60	3	0	no reaction	
6	"	H	40	3	1	34	65:35
7	"	H	80	3	1	47	26:74
8	C_6H_5	H	80	3	1	67	41:59
9	$4\text{-}CH_3O\text{-}C_6H_4$	H	60	4	1	74	26:74
10	$4\text{-}Cl\text{-}C_6H_4$	H	40	3	1	83	50:50
11	$2\text{-}Cl\text{-}C_6H_4$	H	40	3	1	61	56:44
12	1-Naphthyl	H	60	3	1	62	40:60
13	$4\text{-}CH_3\text{-}C_6H_4$	CH_3	60	3	1	70	100:0
14	"	$CH_3\text{-}CH_2\text{-}CH_2$	20	1	1	93	100:0
15	"	$(CH_3)_2CH$	20	1	1	63	100:0
16	"	$CH_3\text{-}CH_2\text{-}CH_2\text{-}CH_2$	20	1	1	60	100:0
17	"	CH_3	0	1	1	26	0:100

a) Summation of isolated yields of 3 and 4.

atom, 1-[N-(4-methylphenyl)]imino-3-thiophthalimide(5), in yield of 83% by the reaction of N-(2-cyanobenzylidene)-4-methylaniline(2) with elemental sulfur in diethylamine.[10)] To confirm the intermediacy of monothiophthalimide(5) in the present reaction, 5 was treated with liquid ammonia at 60 °C for 3 h affording 1,3-diiminoisoindoline(3) and 1-[N-(4-methylphenyl)]-1,3-diiminoisoindoline(4) in yields of 24 and 38%, respectively. This fact implies that both 4-methoxyphenylimino and thiocarbonyl groups in 5 can convert to imino group.[11)]

A plausible pathway of this reaction is consitent with the two important steps, that is, the oxidation of methine carbon of Schiff base and the cyclization. The oxidation of methine carbon with elemental sulfur in liquid ammonia giving thioamide has been already shown.[8)] The cyclization seems to proceed by nucleophilic attack of thiolate anion such as H_2NSS^- toward the nitrile carbon followed by substitution of the sulfur with ammonia as shown in the synthesis of isoindoline from phthalonitrile with elemental sulfur in liquid ammonia (Scheme 2).[6)] Further investigations on the mechanism and application of this reaction are now in progress.



Scheme 2.

References

1) M. Hannack, J. Metz, and G. Pawlowski, Chem. Ber., 115, 2836(1982); G. W. Dirk,T.Inabe,K.F.Schoch,Jr.,and T.J.Marks,J. Am. Chem. Soc.,105,1539(1983).
2) J. A. Elvidge and P. D. Linstead, J. Chem. Soc., 1952, 5008.
3) J. A. Elvidge and R. P. Linstead, J. Chem. Soc., 1952, 5000; P. E. Clark, J. A. Elvidge, and J. H. Golden, ibid., 1956, 4135.
4) H. Hopff and P. Gallegra, Helv. Chim. Acta, 51, 253(1969).
5) P.J.Brach, S.J.Grammatica,O.A.Ossana, and L.Weinberger, J.Heterocycl.Chem., 7, 1403(1970).
6) R.Sato, T.Senzaki, Y.Shikazaki, T.Goto, and M.Saito, Chem. Lett.,1984,1423.
7) R. Sato, T. Senzaki, T. Goto, and M. Saito, Chem. Lett., 1984, 1599.
8) For examples: R.Sato,K.Araya, Y.Takikawa, S.Takizawa, and S.Oae, Phosphorus and Sulfur, 5, 245(1978); R.Sato, T.Sato, K.Segawa,Y.Takikawa, S. Takizawa, and S. Oae, ibid., 7, 217(1979); R.Sato,T.Goto,Y.Takikawa, and S. Takizawa, Synthesis, 1980, 615; R.Sato, T.Etchu, Y.Takikawa, S.Takizawa,and M. Saito, ibid., 1981, 44; R. Sato, S. Chiba, Y. Takikawa, S. Takizawa, and M. Saito, Chem. Lett., 1983, 535; R. Sato, N. Saito, and M. Saito, ibid., 1983, 1603; R.Sato, N.Saito, Y.Takikawa, S.Takizawa, and M.Saito, Synthesis, 1983,1045.
9) The results of micro analysis is as follows. Found:C,71.84;H,5.11;N,16.80%. Calcd for $C_{15}H_{13}N_3O$: C,71.70; H, 5.21; N, 16.72%.
10) Compound 5: Mp 176 °C; ^{1}H-NMR($CDCl_3$) δ=9.00(b,1H),8.10-7.60(m,4H), 7.30-6.90 (m,4H), and 2.37(s,3H). IR(KBr): 3140(>NH), 2850(CH_3), and 1660 cm^{-1}(C=N). Found:C,71.57;H,4.70;N,10.98%. Calcd for $C_{15}H_{12}N_2S$:C,71.40;H,4.80;N,11.10%.
11) M.E. Baguley and J. A. Elvidge, J. Chem. Soc., 1957, 709.

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