CHEMISTRY LETTERS, pp. 1599 - 1602, 1984.

NOVEL SYNTHESIS OF 3-(N-SUBSTITUTED AMINO)-1-ISOINDOLENONES FROM 2-CYANOBENZALDEHYDE WITH AMINES

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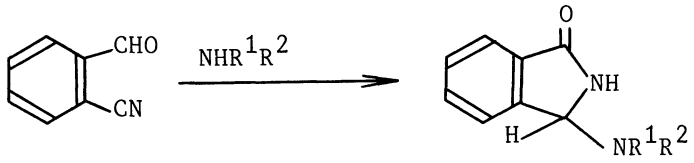
Various 3-(N-substituted amino)-1-isoindolenones were readily synthesized quantitatively by reactions of 2-cyanobenzaldehyde with amines at low temperature such as 20 °C.

Although 2-cyanobenzaldehyde(1) has been used for measurement of activities of enzymes[1] and the synthesis of color materials,[2] a little attention has been paid to the formation of heterocyclic compounds by cyclization of the formyl and cyano groups in 1 with some nucleophiles. Only two examples have been reported; the syntheses of the benzofuran with Grignard reagent[3] and the porphine[4] from 1. On the other hand, it is well known that aromatic aldehydes easily react with amines to give the Schiff bases, but, to our knowledge, there has been no report on the reaction of 1 with amines. Recent study on the reaction of phthalaldehyde with amines by DoMinh et al. has shown the formation of phthalimidines.[5] Moreover, we have recently obtained N,N'-disubstituted 1,3-diiminoisoindolines from phthalonitrile with amines in the presence of elemental sulfur.[6] These facile cyclization with ammonia and amines stimulated us to study the reaction of 1 with amines expecting formation of heterocyclic compounds, 1-isoindolenones. We found now a new type of cyclization of 1 with amines to give 3-(N-substituted amino)-1-isoindolenones(2) at low temperature such as 20 °C in quantitative yields as shown in Eq.1. In this communication, we wish to report preliminarily the ready direct formation of 3-(N-substituted amino)-1-isoindolenones(2). For the preparation of 3-(N-



(1)

1 2

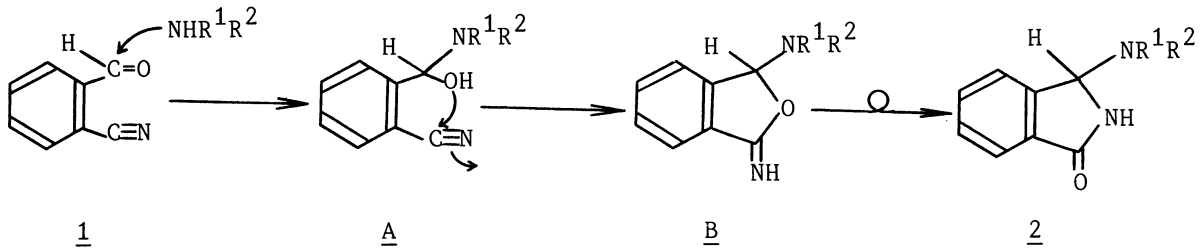
substituted amino)-1-isoindolenones(2), Dunet et al. previously reported a multiple step procedure from phthalonitrile in low total yields.[7] Therefore, the present our method for 2 obviously has advantages in the points of simple procedure and high yields. Typical procedure is as follows: 10 ml of t-butylamine was added to a flask containing 0.5 mmol of 2-cyanobenzaldehyde(1) and the solution was allowed to react with stirring at 20 °C. After completion of the reaction, the amine was removed by evaporation under vacuum. The obtained reaction mixture was chromatographed on silica gel(Wako Gel C-300) using chloroform/methanol(5/1) as eluent giving single product, 3-(N-t-butylamino)-1-isoindolenone(2f), and only trace of recovered 2-cyanobenzaldehyde(1). The structures of isoindolenones(2a-o) were confirmed by NMR, IR, MS and elemental analysis; 2f: ^{1}H NMR($CDCl_3$)δ= 7.83-7.40(4H, m, aromatic), 6.70(1H, broad, NH), 5.50(1H, s, methine), 1.50(1H, broad, NH),and 1.29(9H, s, methyl); IR(KBr) 3310(NH), 3200(NH of lactam), 2970(CH_3), and 1720(CO)cm^{-1} ; MS(70eV), m/z 204. These results are summarized in Table 1.

Various 3-(N-substituted amino)-1-isoindolenones(2a-o) were obtained quantitatively at low temperature such as 20 °C. The isoindolenones bearing bulky groups such as t-butyl(run 6) and cyclohexyl(run 7) were also given in high yields. The formation of isoindolenones which have hydroxyl group and double bond in the molecule is worthy of remark as further synthetic application of the functionalized isoindolenones may be expected (runs 12 and 14). The undesired Schiff base was formed exclusively in the reactions of 1 with neat aromatic amines such as toluidine. The corresponding 1-isoindolenones (2k) was, however, obtained in yield of 16% when methanol was used as solvent (run 11). It is noteworthy that 3-(N,N-disubstituted amino)-1-isoindolenones, 2m, 2n, and 2o, were also obtained in excellent yields by the reactions of 1 with secondary amines such as diethyl- and diallylamines and morpholine. These facts suggest that the nitrogen atom of amide moiety in the isoindolenone is not derived from amine of reagent but from cyano group in the substrate(1).

Table 1. Reactions of 2-Cyanobenzaldehyde(1) with Amines

Run[a]	Amine:R^1R^2NH R^1	R^2	React. temp/°C	React. time/h	Yield of 2/%[b]		Mp/°C(Lit.)
1[c]	H	H	20	2	100	2a	146
2[c]	CH_3-	H	20	1	100	2b	147
3	$CH_3CH_2CH_2$-	H	20	2	100	2c	131
4	$(CH_3)_2CH$-	H	20	3	99	2d	184
5	$CH_3CH_2CH_2CH_2$-	H	20	6	100	2e	127
6	$(CH_3)_3C$-	H	20	36	98	2f	177
7	Cyclohexyl	H	20	9	100	2g	134
8	CH_2=CH-CH_2-	H	20	3	100	2h	133
9	Ph-CH_2-	H	20	10	100	2i	152
10	Ph-CH_2CH_2-	H	20	14	99	2j	144 (145)[7]
11[d,e]	CH_3-C$_6$H$_4$-	H	40	3	16	2k	208 (208)[7]
12	HO-CH_2CH_2-	H	40	1	100	2l	80
13	CH_3CH_2-	CH_3CH_2-	40	1	100	2m	131
14	CH_2=CH-CH_2-	CH_2=CH-CH_2-	20	14	97	2n	93
15	-CH_2CH_2-O-CH_2CH_2-		20	4	100	2o	215
16	Ph-NH-	H	40	1	-	-	
17	HO-	H	40	3	-	-	

a) 0.5 mmol of substrate(1) was served in all cases. b) Isolated yield based on the substrate(1). c) Reaction was carried out in titanium autoclave. d) 10 ml of methanol was used as solvent. e) 0.5 mmol of toluidine was employed.



Scheme 1.

Unfortunately, we could not obtain the corresponding isoindolenones from 1 with phenylhydrazine and hydroxylamine(runs 16 and 17).

Considering that the formyl group in 1 reacts more easily than cyano group with amine and the isoindolenone cannot be essentially obtained from the Schiff base in our system, a plausible pathway may be depicted as shown in Scheme 1. Initial step in this reaction is nucleophilic addition of amine to formyl group affording adduct(A), which cyclizes immediately to B by intramolecular nucleophilic addition of hydroxyl group to cyano group in A followed by conversion to isoindolenone (2).

Finally, the present reaction should provide a new synthetic procedure of γ-lactams. Further synthetic application of the isoindolenones(2a-o) bearing amino group in the molecule is now in progress.

Financial support from The Japan Association of Chemistry is gratefully acknowledged.

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(Received July 3, 1984)