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N-Formylation of Aliphatic Primary Amines with *N*,*N*-Dimethylformamide Promoted by 2,3-Dihydro-1,4-phthalazinedione

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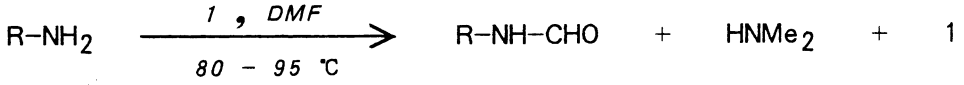
The *N*-formylation of aliphatic primary amine proceeded very effectively in *N*,*N*-dimethylformamide in the presence of restorable 2,3-dihydro-1,4-phthalazinedione.

Although several methods[1] have been reported for *N*-formylation of primary amines by the use of *N*,*N*-dimethylformamide (DMF), there has been no method claimed which utilizes a certain promoter restorable after the workup. We now found that 2,3-dihydro-1,4-phthalazinedione (1) functioned as a renascent promoter in the *N*-formylation of aliphatic primary amines 2 with DMF.



2 3

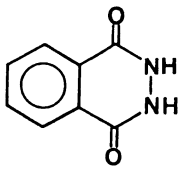
In a general procedure, a suspended mixture of 1 (1.5 mol equiv./-NH_2 group of 2) and 2 in DMF was heated at 80 - 95 °C for more than 40 h and excess DMF was removed under reduced pressure. To the residue, $CHCl_3$ was added and insoluble 1 was collected by filtration. When the filtrate was condensed and the residue was chromatographed on silica gel ($CHCl_3$ / MeOH 9 : 1 v/v), the corresponding formamide 3 was isolated. Some results are listed in Table 1.

N-Formylation occurs in excellent yield and is prevalent to aliphatic primary amines substituted by a primary or secondary alkyl group, while aromatic primary amines can not be formylated. α,ω-Diamine is transformed successfully to α,ω-diformamide (entry 1). The presence of hydroxy and tosylamino groups in the molecule does not affect the formylation (entries 2, 3, 4).

Although the role of 1 in the *N*-formylation mechanism has not been clarified definitively, the formation of a ternary complex among 1, 2, and DMF such as T1 in the transition state is quite possible because 1) the *N*-formylation does not occur effectively in the absence of 1, and 2) dihydrophthalazinedione 1 is known to form weak salts with amines.[2] By the formation of complex T1, both amines 2 and DMF are activated so that the formyl moiety of DMF otherwise sluggish undergoes ready aminolysis by the intramolecular attack of 2. Since T1 is equivalent to the tran-

Table 1. *N*-Formylation of Primary Amines Promoted by 2,3-Dihydro-1,4-phthalazinedione

Entry	Primary amine (2)	Yield/% Formamide (3)
1	$H_2N-(CH_2)_3N(CH_2)_3-NH_2$[a] (Ts)	98
2	$HO-(CH_2)_2-NH_2$	85
3	$TsNH-(CH_2)_2-NH_2$[a]	88
4	$TsNH-(CH_2)_3-NH_2$[a]	89
5	$C_6H_5-CH_2-NH_2$	99
6	$(+)-C_6H_5CH^*(CH_3)-NH_2$	86[b]
7	$(-)-C_6H_5CH^*(CH_3)-NH_2$	86[b]



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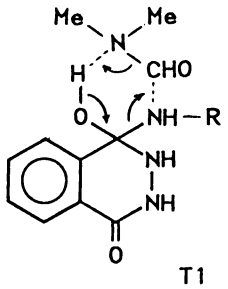

T1

a) Obtained by neutralization of the corresponding hydrochloride salt with $NaHCO_3$. b) At 20 °C, (+)-3 indicated $[\alpha]_D$ +168.3°(c 3.2, $CHCl_3$) and (-)-3, $[\alpha]_D$ -164.0°(c 3.93, $CHCl_3$).

sition state predicted for the conversion of phthalimides to formamides,[3] a mechanistic relationship between the present and the previous *N*-formylation methods is highly interested. Further studies are undertaken and the results will be reported in due course of time.

References

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