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A NEW TRANSFORMATION METHOD OF *N*-ALKYLPHTHALIMIDES TO *N*-ALKYLFORMAMIDES WITH *N*,*N*-DIMETHYLFORMAMIDE AND HYDRAZINE HYDRATE

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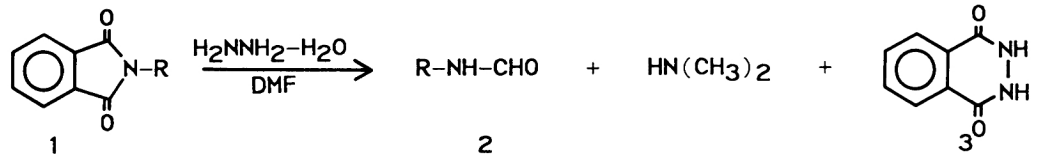
N-Alkylphtalimides were transformed to *N*-alkylformamides, mediated by hydrazine hydrate in *N*,*N*-dimethylformamide, in practical synthetic yields.

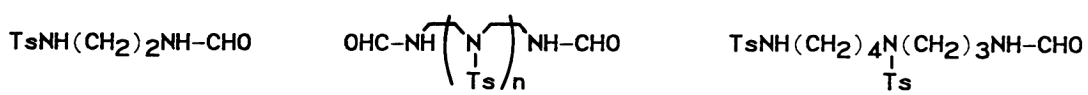
We would like to communicate a new transformation reaction of *N*-alkylphthalimides (1) to *N*-alkylformamides (2) with *N*,*N*-dimethylformamide (DMF) in the presence of hydrazine hydrate, which implies the first practical approach to *N*-formylation of alkyl primary amines with DMF functioning as a formylating reagent.



1 2 3

In a typical procedure, *N*-(3-tosylaminopropyl)phthalimide (1, R=$(CH_2)_3NHTs$)[1] (0.36 g, $1x10^{-3}$ mol) was stirred and heated in DMF (15 ml) in the presence of hydrazine hydrate (0.244 ml, 5 mol equiv. to 1) at ca. 80 °C for 13 h. After removal of excess DMF under reduced pressure, chloroform was added to the residue and the resulting phthalhydrazide (3) (as crystals) was collected by filtration. The filtrate was chromatographed on a silica-gel column eluted with chloroform - methanol (9 : 1 v/v) to give 0.24 g of *N*-formyl-*N*'-tosyl-1,3-propanediamine (2, R=$(CH_2)_3NHTs$) (93% yield); ^{1}H-NMR ($CDCl_3$) δ 8.16 (1H, d, *J*=1.46, -NH-C<u>H</u>O), 6.02 (1H, broad s, -N<u>H</u>-CHO), 5.45 (1H, t, *J*=6.84, -N<u>H</u>-Ts), 3.40 (2H, quar, -C<u>H</u>$_2$-NHCHO), 2.96 (2H, quin, -C<u>H</u>$_2$-NHTs), 2.43 (3H, s, Ar-C<u>H</u>$_3$), and 1.70 (2H, quin, -CH_2-C<u>H</u>$_2$-CH_2-).

Likewise, the transformation reaction was successfully applied to several compounds shown below, in which the products containing one and two formyl groups at the ends were obtained by the reaction of the corresponding monophthalimides and diphthalimides, respectively, which were prepared recently in relation to the study on synthetic polyamine chemistry.[1,2] For the transformation of diphthalimides, 10 mol equiv. of hydrazine hydrate was used.[3]



(77%) 8.16

n=2 (58%) 8.17
n=3 (94%) 8.17

(75%) 8.20

$TsNH(CH_2)_4\underset{\underset{Ts}{|}}{N}(CH_2)_3\underset{\underset{Ts}{|}}{N}(CH_2)_3NH\text{-}CHO$ (72%) 8.20

$OHC\text{-}NH(CH_2)_3\underset{\underset{Ts}{|}}{N}(CH_2)_4\underset{\underset{Ts}{|}}{N}(CH_2)_3NH\text{-}CHO$ (82%) 8.20

These results indicate that the *N*-formylation of phthalimides occurs generally in good yields without resort to the chain length. Since hydrazine is strong nucleophile, the transformation reaction is expected to be applicable to wide range of compounds with the other variety of protective groups resistant to nucleophile. In addition, since the *N*-formyl group was cleaved easily with 2 M-HCl under reflux to give primary amine,[1] *N*-alkylformamides are alkyl primary amine equivalents in synthetic organic chemistry.

Upon consideration of the probable reaction mechanism, any combination of two of three reagents, e.g., phthalimide and DMF or hydrazine and DMF turned out not to generate active intermediate for the group transfer reaction to the third molecule added later to the initial reaction mixture. Furthermore, it was found that compounds with the alkyl primary amino group were not *N*-formylated in the presence of hydrazine in DMF. These preliminary results suggest that a certain intermediate constituted by formylated phthaloylamide-hydrazine complex is formed probably through "basicity dependent group transfer"[4] process between phthalimide, hydrazine, and DMF. For elucidation of the transformation mechanism, further investigation is requisite.

There has been known the *N*-formylation of aromatic primary amines with DMF in the presence of NaOMe.[5] This method, however, is not applicable to alkyl amines at all. The effective *N*-formylation methods of alkyl primary amines known hitherto, particularly in connection with peptide chemistry, are based in principle on employment of formic acid.[6] Therefore, the present transformation reaction not only provides new approach to *N*-formylation of alkyl primary amines, but also extends feasibility of phthalimide protective group in synthetic organic chemistry, taking into account of recent advances in the preparative methods of phthalimides.[1,2,7]

References

1) M. Iwata and H. Kuzuhara, *Chem. Lett.*, submitted.
2) M. Iwata and H. Kuzuhara, *Chem. Lett.*, 1986, 369.
3) Isolated yield in parentheses and chemical shift (in δ ppm) of the formyl proton on ^{1}H-NMR spectrum in $CDCl_3$ are shown; all the structures were confirmed by elemental analyses (C,H,N,S) and ^{1}H-NMR and IR spectra.
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