CHEMISTRY LETTERS, pp. 1195-1198, 1989.

Conversion of Formamides to Alcohols via *N*-Nitrosation

Masaaki IWATA* and Hiroyoshi KUZUHARA
RIKEN (The Institute of Physical and Chemical Research),
Wako, Saitama 351-01

Secondary formamides were found to be favorable sources for the efficient oxygenation site via *N*-nitrosation. Thermal reaction (85 ℃ in benzene) of *N*-nitroso formamides proceeded effectively to provide the corresponding formates in good yields, which, then, were hydrolyzed to alcohols under weakly basic conditions. In treatment of optically active formamide, the corresponding alcohol was isolated with 72% retention of configuration.

Transformation of nitrogen functional groups into oxygen functional groups (oxygenation) is of fundamental importance in synthetic organic chemistry. Although aliphatic primary amines[1] and acetyl- and benzoylated amines[2] have been subjected to oxygenation to alcohols or esters, the traditional methods still suffer from inconsistent product yields or from the formation of such by-products as isomerized products or olefins. We would like to report that formamides (1) which are prepared efficiently by various methods[3] are useful source-functional groups available effectively for oxygenation.

$$\underset{1}{R\text{-}NH\text{-}CHO} \longrightarrow \underset{2}{R\text{-}N(NO)\text{-}CHO} \longrightarrow \underset{3}{R\text{-}O\text{-}CHO} + N_2$$

Sodium nitrite (10 mol equiv per one formamide) was added to a mixture of acetic anhydride (4 part), acetic acid (one part), and 1 at ambient temperature and, then, the whole was stirred for 90 min.[4] To the mixture was added ten volumes of water and the whole was stirred for 60 min. *N*-Nitroso formamide (2) was extracted with a half volume of benzene or toluene and the organic layer was washed four times with water and dried over magnesium sulfate. On TLC (Merck Art 5715, $CHCl_3$: acetone 95 : 5 v/v) the product appeared as clear one spot, indicating complete *N*-nitrosation of 1. After removal of magnesium sulfate by filtration through Celite, the filtrate was stirred and heated at 85 - 95 ℃, while the product formation was monitored on TLC. When 2 disappeared completely, the solvent was evaporated carefully at as low temperature as possible under reduced pressure. The residue was chromatographed on a silica gel column (Merck Art 7734, 0.063 - 0.02 mm) to isolate formates (3). The results are summarized in Table 1.

N-Nitroso formamides (2) were transformed efficiently to the corresponding

formates (3) in more than 40 h, independent of mono- (entries 1-8) or α,ω-di- formamide (entries 9-11). Changes in the reaction time up to 112 h or in the reaction temperature raised up to 95 ℃ by use of toluene did not affect the total results at all. The reaction rate seems rather more dependent on *N*-alkyl substituents of 1; when the formamido group is bound to the secondary alkyl group (entries 7,8), *N*-nitroso formamide (2) disappeared *ca.* 20 times faster than those attached to the primary alkyl group (entry 6). Interest in stereochemistry of the oxygenation reaction made us apply the present procedure to optically pure enantiomers (entries 7,8); through the measurement of the specific rotation of the isolated formate, it was found that the oxygenation proceeded fairly with retention of configuration configuration.[5)]

Table 1. Formation of Formates (3) from Formamides (1) via *N*-Nitrosation

Entry No.	Formamide (1)	Time/h (max.)	Formate/% (3)	olefin/%	^{1}H NMR[a)] δ OCHO
1	PhthN$(CH_2)_4$N$(CH_2)_3$-NH-CHO (Ts)	43 (88)	77	tr	8.00
2	PhthN$(CH_2)_3$N$(CH_2)_3$N$(CH_2)_3$-NH-CHO (Ts, Ts)	63	72	tr	8.04
3	PhthN$(CH_2)_3$N$(CH_2)_4$N$(CH_2)_3$-NH-CHO (Ts, Ts)	64 (112)	75	tr	8.04
4	PhthN$(CH_2)_4$N$(CH_2)_3$N$(CH_2)_3$-NH-CHO (Ts, Ts)	44 (92)	73	18	8.04
5	PhthN$(CH_2)_3$N$(CH_2)_3$N$(CH_2)_4$-NH-CHO (Ts, Ts)	40 (73)	79	tr	8.04
6	$C_6H_5CH_2$NH-CHO	41	40[b)]	(toluene)	8.15
7	(+) $C_6H_5CH^*(CH_3)$NH-CHO	2	32[b,c)]		8.09
8	(-) $C_6H_5CH^*(CH_3)$NH-CHO	2	33[b)]		8.09
9	OHC-NH$(CH_2)_3$N$(CH_2)_4$N$(CH_2)_3$NH-CHO (Ts, Ts)	46 (73)	75		8.04
10	OHC-NH$(CH_2)_3$N$(CH_2)_3$N$(CH_2)_3$NH-CHO (Ts, Ts)	73 (110)	72		8.04
11	OHC-NH$(CH_2)_3$N$(CH_2)_3$NH-CHO (Ts)	40	85		8.03

a) Recorded on JEOL GSX500S (500 MHz) instrument with Me_4Si as the internal standard (δ in ppm). b) Since the products were very volatile, it was hard to determine exact product yields by isolation; on TLC, actual yields seems much better (see also Footnote c) in Table 2). c) See, Ref. 5.

The other characteristics of the conversion method of formamide to formate are implicated to the side reactions, olefin formation and denitrosation reaction of 2 as pointed in general in the transformation of *N*-nitrosated sulfonamides[6)]

and acylamides.[2] In entries 1 through 5, all the spots on TLC were isolated carefully and the structures of products were analyzed. It turned out that (a) the corresponding terminal olefin was the sole by-product, produced generally in trace amount (entries 1,2,3,5) and, at most, in less than 18% yield (entry 4); (b) neither denitrosation back to the formation of 1 nor any isomerization in the alkyl group was detected at all. In sum, quantitative *N*-nitrosation of formamides and subsequent thermal reaction provide an alternative route much better and synthetically more feasible in all respects than the conventional oxygenation methods of nitrogen functional groups.

Additional advantage lying in the oxygenation through the formamide route is obvious in hydrolysis of formates; Table 2 shows three preliminary methods for hydrolysis. When ω-phthalimidated formate was heated with hydrazine hydrate (10 mol equiv) in DMF (entry 12), ω-formamido alcohol was produced in excellent yield since phthalimides are transformed to formamides under the conditions.[3e] Methods B and C are more feasible in general use owing to the operational simplicity; in the method B, one or two drops of saturated ammonia water was mixed, while, in the method C, moistened ammonia gas was mixed, which was taken out 4 to 10 times with 2 mL volume of a pipette from the upper atmosphere of the bottle containing saturated ammonia water allowed to stand right after vigorous shake.

Table 2. Preliminary Typical Hydrolysis Methods of Formates (3) to the Corresponding Alcohols

Entry	Formate (3)	Alcohol/%	Method[a]
12	$PhthN(CH_2)_4N(CH_2)_3$-O-CHO (Ts)	96	A[b]
13	OHC-O-$(CH_2)_3N(CH_2)_4N(CH_2)_3$-O-CHO (Ts, Ts)	87	B
14	OHC-O-$(CH_2)_3N(CH_2)_3N(CH_2)_3$-O-CHO (Ts, Ts)	89	B
15	$C_6H_5CH_2$-O-CHO	47[c]	C
16	(+) $C_6H_5CH^*(CH_3)$-O-CHO	52[c]	C
17	(-) $C_6H_5CH^*(CH_3)$-O-CHO	46[c]	C

a) Methods: A $N_2H_4 \cdot H_2O$ / DMF, 85 °C / 27 h, B 28%-NH_4OH / MeOH, r.t. / 1 h, C Moistened NH_3 gas / MeOH, r.t. / overnight. b) By this method, the product obtained was the corresponding ω-formamido alcohol (see Ref. 3e). c) On account of volatility of the preceding formates, yields shown are based on the corresponding amine (entry 15) and formamides (entries 16, 17); on TLC, the hydrolysis proceeded in excellent yields: see also Ref. 7.

Since hydrolysis of formates proceeds 100 times faster than acetates[8] and even much faster than benzoates, selective cleavage of formate ester in the presence of acetate and benzoate will be made possible; thus, the total transformation process described in the present report will function strategically in syn-

thetic fields relevant to amine and alcohol functional groups. Although we have not described the significance of the compounds subjected to transformation above, most of them are natural polyamine derivatives. In particular, α,ω-diol produced in entry 13 is latent "spermindiol" which enhances enzymic activity for DNA hydrolysis and RNA degradation.[9] The present approach provides an efficient method for the synthesis of alcoholic analogues of natural polyamines, spermidine, spermine, thermine, and thermospermine.

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4) When the previous *N*-nitrosation conditions described in the report [M. Iwata and H. Kuzuhara, Bull. Chem. Soc. Jpn., 58, 3395 (1985)] were applied, formamide was nitrosated incompletely. Formamides employed were obtained as follows; ω-phthalimidated formamides (entries 1-5) were prepared according to the method reported lately: *Idem.*, *ibid.*, 62, 1102 (1989). α,ω-Diformamides (entries 9-11) were prepared according to the method reported [*Idem.*, *ibid.*, 62, 198 (1989)]. Formamides (entries 6-8) were prepared from the corresponding amines according to the newly developed method which will be reported elsewhere.
5) Specific rotation data for optically pure α-phenylethyl formates have been unknown. The product isolated in entry 7 indicated the specific rotation $[\alpha]_D$ +71.0°: c 3.67, $CHCl_3$ at 20 °C. For comparison, structurally related (-)-α-phenylethyl acetate has $[\alpha]_D$ -127.6°; P. A. Levene and R. E. Marker, J. Biol. Chem., 97, 379 (1932).
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7) The specific rotation of the alcohol (entry 17) was measured to be -18.23° (c 0.867, MeOH at 20 °C), which indicates 44.1% e.e. on the basis of that value reported for the pure enantiomer: R. H. Pikard and J. Kenyon, J. Chem. Soc., 99, 45 (1911).
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(Received April 22, 1989)