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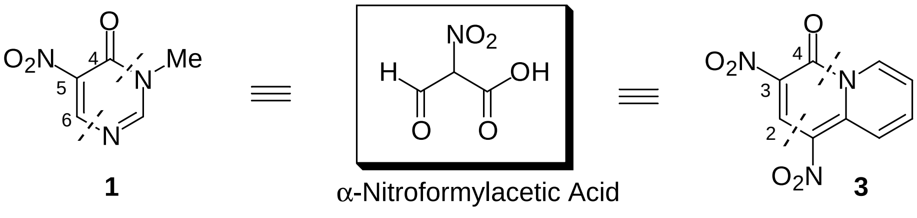
SYNTHETIC EQUIVALENT OF α-NITROFORMYLACETIC ACID

Nagatoshi Nishiwaki,*[a] Hiromi Ohtomo,[a] Mina Tamura,[a] Kazushige Hori,[b]
Yasuo Tohda,[b] and Masahiro Ariga*[a]

a Department of Chemistry, Osaka Kyoiku University,
b Division of Natural Science, Osaka Kyoiku University,
Asahigaoka 4-698-1, Kashiwara, Osaka 582-8582, Japan

Abstract - A novel synthetic procedure for 3-nitro-2-pyridone derivatives (**2**) is provided, which includes the ring transformation of 1,3-dinitroquinolizin-4-one (**3**) with ketones in the presence of ammonium acetate.

3-Methyl-5-nitropyrimidin-4(3*H*)-one (**1**) possesses a suitable structure for two kinds of ring transformations leading to 3-nitro-2-pyridones (**2**) and 4,5-disubstituted pyrimidines.[1] Pyrimidinone (**1**) behaves as the synthetic equivalents of α-nitroformylacetic acid (C4-C5-C6) in the former case and activated diformylamine (C2-N1-C6) in the latter case. It is, however, difficult to control two ring transformations. Since nitropyridone (**2**) is a pharmaceutically important skeleton,[2] it is highly valuable to develop a new synthetic method affording **2** exclusively. We pay attention that 1,3-dinitroquinolizin-4-one (**3**)[3] has a common partial structure (C2-C3-C4) to **1**, and **3** is regarded to be a fused 2-pyridone in which one of three reactive points is blocked with a benzene ring.[4] These features prompt us to study the ring transformation of quinolizinone (**3**) with ketones aimed at the selective synthesis of nitropyridones (**2**).



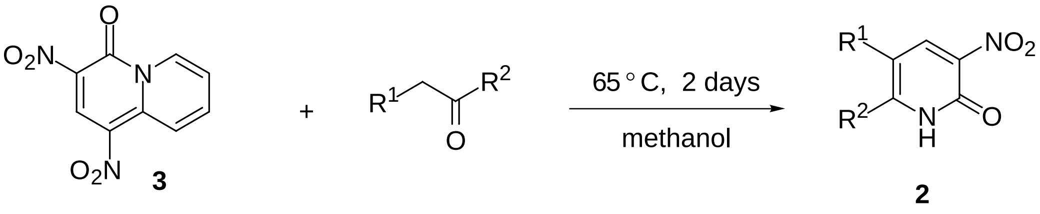
1

α-Nitroformylacetic Acid

3

Ammonium acetate was employed as a nitrogen source and as an activating agent of the carbonyl group. Several solvents were screened for the reaction of **3** with acetophenone. In cases of pyridine and ethanol, quantitative recovery of quinolizinone (**3**) was observed. On the other hand, the reaction in THF or acetonitrile gave a complicated mixture. Phenyl substituted pyridone (**2a**) was isolated in 18 % yield when methanol was used as the solvent (run 1). The present reaction was considerably affected by the amount of ammonium salt. Larger amounts of ammonium acetate improved the yield of **2a** up to 49 % (runs 2-4). Ammonium benzoate was also found to be available for this reaction to give **2a** in a similar yield.

Other ketones were employed instead of acetophenone (runs 5-10). Significant difference in the reactivity was not observed among *p*-substituted acetophenones. The present reaction was also applicable to aliphatic ketones to furnish corresponding pyridones (**2e-g**) in moderate yields. It was noteworthy that sterically



run	R^1	R^2		NH_4OAc / equiv.	Yield / %
1	H	Ph	**a**	2	18
2	H	Ph		4	31
3	H	Ph		6	45
4	H	Ph		8	49
5	H	*p*-$MeOC_6H_4$	**b**	8	41
6	H	*p*-MeC_6H_4	**c**	8	47
7	H	*p*-$NO_2C_6H_4$	**d**	8	35
8	H	Me	**e**	8	58
9	H	*i*-Pr	**f**	8	23
10	—$(CH_2)_5$—		**g**	8	26

hindered substituents, such as aryl or *i*-Pr groups, could be introduced into the pyridone ring.

Although the optimization of reaction conditions should be performed still more, only single ring transformation proceeded affording 3-nitro-2-pyridones (**2**). This reaction will be a novel methodology in the synthetic chemistry for nitropyridone systems.

EXPERIMENTAL

Typical procedure: To a solution of quinolizinone (**3**, 235 mg, 1 mmol) in methanol (20 mL), were added acetophenone (0.23 mL, 2 mmol) and ammonium acetate (620 mg, 8 mmol), and the mixture was heated at 65 °C for 2 days. During the reaction, yellow needles were precipitated. This crystalline product was collected by filtration to furnish nitropyridone (**2a**) in 49 % yield (106 mg, 0.49 mmol).

Reactions of **3** with other ketones were similarly conducted. All of nitropyridones (**2a-g**) gave satisfactory spectral and analytical data.[1]

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