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A Convenient Method for Synthesizing Modified 4-Nitrophenols

Yumi Nakaike, Yoshio Kamijo, Satoshi Mori, Mina Tamura, Nagatoshi Nishiwaki,* and Masahiro Ariga*

Department of Chemistry, Osaka Kyoiku University, Asahigaoka 4-698-1, Kashiwara, Osaka 582-8582, Japan

nishi@cc.osaka-kyoiku.ac.jp

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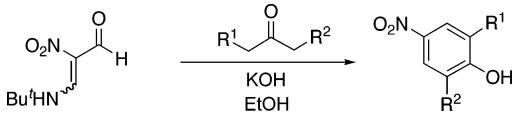
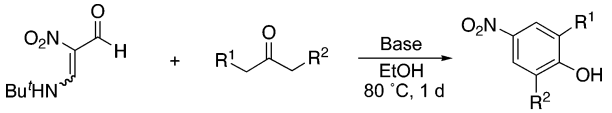


β-Nitroenamine having a formyl group behaves as the synthetic equivalent of unstable nitromalonaldehyde upon treatment with ketones under basic conditions and leads to 2,6-disubstituted 4-nitrophenols. The present method is safer than the conventional one using sodium nitromalonaldehyde and enables the preparation of hitherto unknown nitrophenols.

4-Nitrophenol derivatives **1** (see Scheme 1) reveal versatile utilities for functional materials such as dyes,[1] pharmaceutical agents,[2] or their synthetic intermediates. In the industrial process, substituted nitrophenols are prepared by Friedel−Crafts alkylation followed by nitration.[3] Friedel−Crafts reaction is a useful method for C−C bond formation on the benzene ring;[4] however, it suffers from several disadvantages. Low regioselectivity of the alkylation has not been overcome satisfactorily, although energetic study has been performed on development of catalysts for the alkylation.[5] In addition, normal alkyl groups longer than the ethyl group cannot be introduced since the intermediate carbonium ion causes rearrangement. The arylation[6] and the monoalkylation of the benzene ring also are not easily achieved.

As another methodology for construction of nitrophenols **1**, a building block having a nitro group is built in the framework upon treatment with ketones.[7,8] Nitromalonaldehyde (**NMA-H**) often appears as the synthon in retrosyntheses for a variety of nitro compounds, but it cannot actually be employed because of instability. Thus, its sodium salt (**NMA-Na**) has been used as the synthetic equivalent of **NMA-H** from old time.[7] The salt **NMA-Na** is prepared from furfural via mucobromic acid with somewhat troublesome manipulations, and the insolubility of **NMA-Na** in general organic solvents obliges us to conduct reactions in aqueous medium or in a highly polar solvent.[9] Furthermore, crude **NMA-Na** is impact-sensitive and thermally unstable and should be handled as a potentially explosive material. Despite some serious problems mentioned here, **NMA-Na** is widely used even now in organic syntheses because of the absence of any other efficient reagents.

SCHEME 1. Syntheses of Modified Nitrophenols



3 **4** **1**

From this viewpoint, we have shown two reagents that behave as the synthetic equivalent of **NMA-H**. When 3,5-dinitro-2-pyridone (**2**) was heated with ketones in the presence of ammonia, the ring transformation proceeded to give 5,6-disubstituted 3-nitropyridines accompanied by elimination of anionic nitroacetamide.[10] On the other hand, our recent attention has been paid to 3-*tert*-butylamino-2-nitro-2-propenal (formylnitroenamine **3**, see Scheme 1), which is readily prepared by aminolysis of 1-methyl-5-nitro-2-pyrimidinone followed by half hydrolysis.[11] Nitro-substituted pyrazoles, isoxazole, pyrrole, pyrimidines, and diazepines could be easily synthesized upon treatment of **3** with hetero dinucleophiles.[12] Nitroenamine **3** is superior to **NMA-Na** and dinitropyridone **2** with regard to treatability, since **3** is soluble in almost all general organic solvents and is not explosive. These results prompted us to study the condensation of **3** with carbon dinucleophiles for improvement of synthetic utility

* To whom correspondence should be addressed. Tel: 81-729-78-3399. Fax: 81-729-78-3399.

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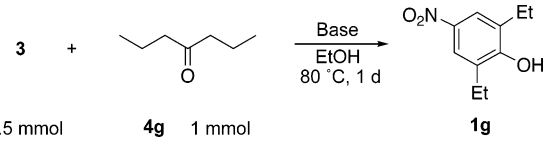
TABLE 1. Syntheses of Functionalized Nitrophenols

run	R^1	R^2	ketone	base	product (yield, %)
1	COOEt	COOEt	**4a**	NEt_3	**1a** (80)
2	COOEt	H	**4b**	NaOEt	**1b** (55)
3	COOMe	OMe	**4c**	NaOEt	**1c** (51)
4[a]	COMe	H	**4d**	NaOEt	**1d** (0)
5[b]	COPh	H	**4e**	NaOEt	**1e** (0)

[a] 26% 4-nitrophenol was obtained. [b] 18% 4-nitrophenol was obtained.

TABLE 2. Optimization of Reaction Conditions



run	base	solvent (cm^3)	yield of **1g** (%)
1	NEt_3	EtOH (10)	0
2	$KOBu^t$	*t*-BuOH (10)	58
3	$KOBu^t$	*t*-BuOH (5)	86
4	NaOEt	EtOH (5)	90
5	KOH	EtOH (10)	43
6	KOH	EtOH (5)	87
7	KOH	EtOH (2)	quant

of **3**. The present paper provides a new method for synthesizing modified 4-nitrophenols **1**, which were not easily available by alternative procedures.

When nitroenamine **3** was allowed to react with diethyl 3-oxopentanedioate (**4a**) in the presence of triethylamine, the double condensation readily proceeded at room temperature to afford 2,6-bis(ethoxycarbonyl)-4-nitrophenol (**1a**)[10] in 80% yield (Table 1, run 1). To the contrary, substrates having only one active methylene group such as ethyl 3-oxobutanoate (**4b**) caused no change under the same conditions. In such case, sodium ethoxide was the effective base, furnishing nitrophenol **1b**[10] (run 2). It was also possible to introduce a methoxy group besides an ester function when keto ester **4c** was employed (run 3). On the other hand, deacylation occurred to give unsubstituted nitrophenol **1f** (R^1, R^2 = H) in the cases of diketones **4d** and **4e** without detection of corresponding products **1d** and **1e** (runs 4 and 5). The similar reactions were conducted at low temperature to avoid the deacylation; however, no formation of desired products was observed. Furthermore, the use of less nucleophilic butoxide as the base also was not effective.

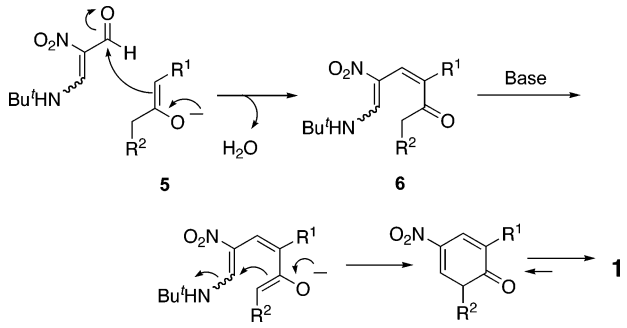
To extend the scope of substrate for this reaction, simple ketones **4g**−**p** were employed instead of 1,3-dicarbonyl compounds. At first, synthesis of 2,6-diethyl-4-nitrophenol (**1g**) from **3** and 4-heptanone (**4g**) was studied using several kinds of bases. Although triethylamine caused no reaction (Table 2, run 1), alkoxides, especially ethoxide, were found to be effective bases (runs 2−4). It was also possible to use more treatable potassium hydroxide (runs 5−7). Although sodium hydroxide showed similar reactivity, potassium hydroxide was somewhat preferable with regard to solubility in ethanol. The present reaction was considerably affected by the concentration of reagents; thus diminution of solvent improved the yield of **1g** (runs 2, 3, and 5−7). The tendency was remarkable in the case of potassium hydroxide, and the quantitative conversion to **1g** was consequently achieved (run 7). The optimized conditions were applicable to a large-scale reaction without significant decrease of the yield, namely, nitrophenol **1g** was obtained in 91% yield from 1 gram of nitroenamine **3**.

TABLE 3. Syntheses of 2,6-Disubstituted Nitrophenols 1h−p

run	R^1	R^2	ketone	base	yield (%)
1	Me	Me	**h**	NaOEt	87[7]
2	H	*i*-Pr	**i**	KOH	quant[2a]
3	*i*-Pr	*i*-Pr	**j**	KOH	12[8]
4	H	Pr	**k**	KOH	quant
5	Pr	Pr	**m**	KOH	63
6	Pr	Pr	**m**	NaOEt	quant
7[a]	Ph	Ph	**n**	KOH	77[1]
8	Ph	Ph	**n**	NaOEt	91
9	Et	Me	**o**	KOH	67[7]
10	Et	Me	**o**	NaOEt	74
11[a]	Ph	Pr	**p**	KOH	55
12	Ph	Pr	**p**	NaOEt	76

[a] Three days.

SCHEME 2. Plausible Mechanism for the Present Reaction



Modification of the nitrophenol skeleton could be performed by use of other ketones **4h**−**p** (Table 3). Whereas the nitrophenol having an isopropyl group, **1i**, was easily obtained from **3** and 4-methyl-2-pentanone (**4i**) (run 2), only small amount of diisopropyl product **1j** was formed with complication of the reaction mixture, which was probably due to steric hindrance of ketone **4j** (run 3). A similar tendency was also observed when **4k** and **4m** were used (runs 4 and 5). In the latter case, phenol **1m** was obtained in almost pure form, which means that water-soluble byproducts were formed.

It was considered that the present reaction was initiated with attack of enolate **5** to the formyl group of **3** giving Knoevenagel-type intermediate **6**, and the following condensation proceeded intramolecularly to form nitrophenol **1** (Scheme 2). In consideration of the quite different reactivities mentioned above (runs 2−5), the first intermolecular condensation suffer from bulkiness of the enolate ion **5**. To the contrary, the bulkiness of the substrate did not prevent the second condensation in **6** because of intramolecular process.

Introduction of a propyl or a phenyl group to the benzene ring was also performed, furnishing nitrophenols **1k**−**n** (runs 4−8). Furthermore, the use of unsymmetrical ketones enabled the construction of unsymmetrical nitrophenols **1o** and **1p**, those having different substituents at the 2- and the 6-positions (runs 9−12).

In summary, the present reaction afforded modified nitrophenols **1** whose substituents were not readily

introduced by Friedel−Crafts alkylation. Although similar condensation of **NMA-Na** with ketones is possible,[7] nitroenamine **3** is more easily handled, which requires only simple experimental manipulations with considerable safety.[12] In addition, this procedure will be effective for ketones insoluble in aqueous media that cannot be used for reactions using **NMA-Na**. Hence, the use of nitroenamine **3** realized the syntheses of various nitrophenols including hitherto unknown derivatives, and the synthetic utility of **3** was significantly improved.

Experimental Section

Synthesis of Nitrophenol 1g. To a solution of nitroenamine **3** (86 mg, 0.5 mmol) and 4-heptanone **4g** (140 μL, 1 mmol) in ethanol (1.5 mL) was added a solution of base (1 mmol) in ethanol (0.5 mL). The resultant mixture was heated at 80 °C for 1 day, and the reaction was quenched with 1 M hydrochloric acid (1.0 mL, 1 mmol). After removal of the solvent in vacuo, the residue was extracted with dichloromethane (10 mL × 3). The organic layer was dried over magnesium sulfate and concentrated to afford nitrophenol **1g** (98 mg, 0.5 mmol, quant) as a yellow solid. The obtained nitrophenol **1g** was confirmed to be pure, and further purification was performed by column chromatography on silica gel using hexane−ethyl acetate (98/2) as the eluent. When other carbonyl compounds **4** were employed, the corresponding nitrophenols were prepared in a similar way.

2-Methoxy-6-methoxycarbonyl-4-nitrophenol (1c). White powder; mp 146−148 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 4.01 (s, 3H), 4.04 (s, 3H), 7.87 (d, J = 2.5 Hz, 1H), 8.43 (d, J = 2.5 Hz, 1H), 11.74 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 53.2 (q), 56.7 (q), 110.2 (d), 113.7 (s), 117.8 (d), 139.5 (s), 149.0 (s), 157.3 (s), 169.7 (s); IR (KBr/cm^{-1}) 1684, 1523, 1336. Anal. Calcd for $C_9H_9NO_6$: C, 47.58; H, 3.99; N, 6.17. Found: C, 47.58; H, 3.94; N, 6.15.

4-Nitro-2-propylphenol (1k). White powder; mp 48−50 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.00 (t, J = 7.3 Hz, 3H), 1.69 (tq, J = 7.5, 7.3 Hz, 2H), 2.65 (t, J = 7.5 Hz, 2H), 5.6−5.9 (br, 1H), 6.86 (d, J = 8.8 Hz, 1H), 8.02 (dd, J = 8.8, 2.7 Hz, 1H), 8.07 (d, J = 2.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 13.8 (q), 22.3 (t), 31.7 (t), 115.2 (d), 123.6 (d), 126.1 (d), 129.6 (s), 141.5 (s), 159.3 (s); IR (KBr/cm^{-1}) 3500−3200, 1494, 1338. Anal. Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.56; H, 6.40; N, 7.73.

2,6-Dipropyl-4-nitrophenol (1m). White powder; mp 89−90 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.00 (t, J = 7.4 Hz, 6H), 1.69 (tq, J = 7.5, 7.4 Hz, 4H), 2.64 (t, J = 7.5 Hz, 4H), 5.6−5.8 (br, 1H), 7.92 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 13.3 (q), 22.4 (t), 31.9 (t), 123.6 (d), 128.6 (s), 140.9 (s), 157.6 (s); IR (KBr/cm^{-1}) 3600−3400, 1506, 1331. Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.24. Found: C, 64.20; H, 7.72; N, 6.26.

4-Nitro-2-phenyl-6-propylphenol (1p). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.00 (t, J = 7.3 Hz, 3H), 1.71 (tq, J = 7.5, 7.3 Hz, 2H), 2.70 (t, J = 7.5 Hz, 2H), 6.0−6.1 (br, 1H), 7.43 (dd, J = 7.3, 6.9 Hz, 2H), 7.45 (t, J = 6.9 Hz, 1H), 7.51 (d, J = 7.3 Hz, 2H), 7.99 (d, J = 2.6 Hz, 1H), 8.03 (d, J = 2.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 13.9 (q), 22.4 (t), 32.2 (t), 123.7 (d), 125.0 (d), 128.3 (s), 129.0 (d), 129.0 (d), 129.8 (d), 130.5 (s), 135.0 (s), 140.6 (s), 156.2 (s); IR (KBr/cm^{-1}) 3500−3400, 1495, 1330. Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.19; H, 6.09; N, 5.16.

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