

New One-Pot Synthesis of 4-Hydroxybenzaldehyde Derivatives and Picric Acid from 4-Hydroxyphenylglycine with HNO₃/H₂O

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Since aromatic aldehydes are important intermediates in the chemical, pharmaceutical and cosmetic industries, easy and convenient synthetic methods to synthesize them have been pursued. Among the most widely-used methods are formylation of aromatic compounds and oxidation of primary alcohols. Previous reports describe a variety of formylation reagents, including formyl fluoride HCOF and BF₃,¹ dichloromethyl methyl ether and AlCl₃,² formamides and phosphorus oxychloride (Vilsmeier-Haack reaction),³ Zn(CN)₂ and HCl (Gatterman reaction),⁴ NaCN and super acidic conditions (F₃CSO₂OH-SbF₅),⁵ while various oxidizing agents, such as Na₂Cr₂O₇ in water,⁶ K₂Cr₂O₇ in DMF,⁷ CrO₃ on silica gel,⁸ NCS-TEMPO,⁹ tetrapropylammonium permuthenate (TPAP)¹⁰ and nitroxyl radical oxidizing agent,¹¹ have been utilized to convert primary alcohols to aldehydes.

Interestingly, along with these general methods for the synthesis of aromatic aldehydes, the conversion of aromatic amino acids into aromatic aldehydes has also been pursued.¹² Hendel and co-workers recently reported that 4-hydroxyphenylglycine was diazotized in an acidic medium with sodium nitrite, followed by hydration to afford corresponding mandelic acid,¹³ which was then transformed into 4-hydroxybenzaldehyde in the presence of metal or hydroxide as a catalyst (Scheme 1).¹⁴

Other methods such as oxidation of hydroxyphenylglycine using metal catalysts or the coupling reaction of aromatic amino acid and pyruvic acid derivatives also generated corresponding aromatic aldehydes, but these methods resulted in low yields due to a high proportion of by-products.¹⁵ Despite the numerous methods for synthesizing various aromatic aldehydes reported in the literature, the significant drawbacks to these methods have created a demand for an improved method. For example, the previously reported methods, such as formylation, require long-reaction times, toxic reagents, and tedious workup procedure. A more serious drawback is that the products of these methods are usually a mixture of the desired formyl compound with the undesired carboxylic acid compound.

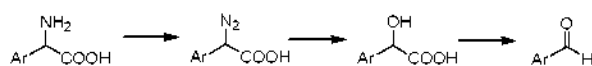
In recent years, we have explored the use of substituted 4-hydroxyphenylglycines (4-HPG) as building blocks for the development of new peptide drugs. During these studies, we were surprised by our observation that 4-HPG was converted into 4-hydroxybenzaldehyde (4-HBA) under HNO₃/H₂O system in a

single step with high purity. Moreover, we could transform 4-HPG into 4-HBA, 3-nitro-4-HBA, 3,5-dinitro-4-HBA, or picric acid by altering the reaction temperatures and times. Herein, we describe this efficient one-pot method to synthesize 4-HBA and its derivatives from 4-HPG using aqueous nitric acid.

We initially identified this method while attempting to synthesize 3-nitro-4-HPG from 4-HPG using standard nitration conditions.¹⁶ To our surprise, when we reacted 4-HPG with 20% nitric acid at 40 °C for 12 hr, we obtained 3-nitro-4-HBA instead of 3-nitro-4-HPG. This unexpected result prompted us to investigate whether nitration in aromatic ring is occurred prior to the conversion of the amino acid group in 4-HPG into the aldehyde group. When 4-HPG was reacted with 20% nitric acid at room temperature for 1 hr, 4-HBA was obtained almost exclusively (4-HBA : 3-nitro-4-HBA = 93 : 7). However, when the reaction was extended to 24 hr, 4-HBA was gradually nitrated to yield a higher proportion of 3-nitro-4-HBA (4-HBA : 3-nitro-4-HBA = 48 : 52). This result confirmed that 4-HPG was first converted into 4-HBA, which was then nitrated to afford 3-nitro-4-HBA by electrophilic aromatic substitution.

With these initial results in hand, we next examined reaction parameters, such as nitric acid concentration, reaction temperature, and reaction time, to determine optimal conditions for selective preparation of 4-HBA, 3-nitro-4-HBA and 3,5-dinitro-4-HBA. The results are summarized in Table 1. Four different nitric acid concentrations (50%, 20%, 10%, and 5%) were first tested with 4-HPG at room temperature for 12 hr (entries 1-4). As expected, the higher nitric acid concentrations yielded more 3-nitro-4-HBA than 4-HBA, while the 10% nitric acid concentration condition produced a limited amount of pure 4-HBA product with a large quantity of unreacted starting material. The optimal condition for selective 4-HBA formation was identified when the reaction was conducted with 20% nitric acid concentration at room temperature for 12 hr. Despite a large quantity of starting material recovered under this condition, it resulted in 50% yield, the highest we observed (entry 3).

The reaction temperature had a profound effect on the conversion of 4-HPG into the corresponding aldehyde derivatives in the presence of 50% nitric acid. Even though an approximate 1:1 mixture of 4-HBA and 3-nitro-4-HBA was obtained from the reaction conducted at room temperature for 12 hr, the same reaction conducted at 60 °C for 12 hr afforded pure 3-nitro-4-HBA in 85% yield (entry 5). This reaction condition was successfully applied to the syntheses of 5-substituted-3-nitro-HBA derivatives. As a result, when 3-chloro-4-HPG and 3-bromo-4-HPG were reacted with 50% nitric acid at 60 °C for 12 hr, the



Scheme 1

Table 1. Reaction of 4-hydroxyphenylglycine derivatives with HNO₃/H₂O conditions.

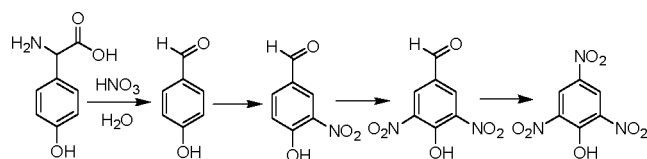
(R = H, Cl, Br)

Entry	Substrate	Temp. (°C)	Time (hr)	HNO ₃ conc.	Products	Yield (%)
1		r.t.	12	5%		11
2		r.t.	12	10%		18
3		r.t.	12	20%		50
4		r.t.	12	50%	+	39 : 34
5		60	12	50%		85
6		60	24	50%		77
7		60	12	50%		72
8		60	12	50%		70
9		reflux	12	50%		80
10		reflux	3	50%		91
11		reflux	1	50%		87

corresponding aldehydes were obtained in 72% and 70% yields, respectively (entries 7-8). However, when the reaction was extended to 24 hr, 3,5-dinitro-4-HBA was obtained as the major product in 77% yield (entry 6).

For the purpose of reducing the reaction time, reflux condition

was also investigated with our system. Surprisingly, our optimized reflux conditions completely converted 4-HPG into 3,5-dinitro-4-HBA within 1 hr, which was eventually converted into picric acid when the reaction was extended to 12 hr (entry 9). Although we have not established the exact mechanism for the



Scheme 2

formation of picric acid. to the best of our knowledge, this result was the first example of synthesis of picric acid from the aromatic amino acid compound in a single step. The similar results were also obtained when 4-HBA and 3-nitro-4-HBA were reacted with 50% nitric acid for 12 hr under reflux condition. As an extension of these results, when the same reflux condition was applied to 3-chloro-4-HPG and 3-bromo-4-HPG, the corresponding 2-chloro-4,6-dinitrophenol and 2-bromo-4,6-dinitrophenol were successfully produced with good yields (entry 10-11). It is of interest to note that 3-nitro-4-HPG, our initial objective compound, was synthesized under diethyl ether/ HNO_3 condition. Therefore, as shown in Scheme 2, 4-HPG can be selectively transformed into 4-HBA, its nitro derivatives, picric acid, or 4-nitro-HPG with aqueous nitric acid in a single step, simply by selecting appropriate reaction conditions.

In summary, we have discovered a novel, one-pot procedure for synthesizing 4-HBA, various 4-nitro-HBA derivatives, and picric acid from 4-HPG by using $\text{HNO}_3/\text{H}_2\text{O}$ system. This method is the first report to describe a method for synthesizing various aromatic aldehydes and picric acid from an aromatic amino acid using simple aqueous acid condition. Our method has advantages over previously-described methods due to a simple work-up procedure, high product purity, good yields, and a cheap water solvent system.

Experimental Sections

^1H -NMR and ^{13}C -NMR spectra were recorded on a Varian Mercury 400 spectrometer. Melting points were determined on a Fisher-Johns melting point apparatus and were uncorrected. Mass spectra were measured on a Shimadzu LCMS-2010EV (Chiyoda-Ku, Tokyo, Japan) mass spectrometer.

General procedure for the preparation of 3-nitro-4-hydroxybenzaldehyde from 4-hydroxyphenylglycine. 4-Hydroxyphenylglycine (500 mg, 2.99 mmol) and nitric acid (5 mL) in water (5 mL) were stirred at 60 °C. After 12 hr, the reaction mixture was cooled to 0 °C. The precipitate was filtered, washed with diethyl ether, and dried to afford the product as a yellow solid (425 mg, 85%).

4-Hydroxybenzaldehyde (3): mp: 114 ~ 115 °C (reference¹⁷: 116 °C); ^1H NMR (CDCl_3) δ 9.79 (s, 1H), 7.83 (d, 2H), 6.92 (d, 2H); ^{13}C NMR (CDCl_3) δ 190.14, 136.30, 131.81, 128.40, 115.78; ESI-MS: M-H^- (m/z) 121.

4-Hydroxy-3-nitrobenzaldehyde (5): mp: 142 ~ 143 °C; ^1H NMR (CDCl_3) δ 9.92 (d, 1H), 8.39 (d, 1H), 7.98 (q, 1H), 7.24 (d, 1H); ^{13}C NMR (CDCl_3) δ 189.91, 156.64, 136.94, 134.16, 128.07, 127.62, 119.61; ESI-MS: M-H^+ (m/z) 166.

4-Hydroxy-3,5-dinitrobenzaldehyde (6): mp: > 270 °C; ^1H NMR (CDCl_3) δ 9.58 (s, 1H), 8.21 (s, 2H); ^{13}C NMR (CDCl_3) δ 186.84, 162.08, 142.52, 131.19, 114.30; ESI-MS: M-H^- (m/z) 211.

3-Chloro-4-hydroxy-5-nitrobenzaldehyde (7): mp: 158 °C; ^1H NMR ($\text{DMSO-}d_6$) δ 9.84 (s, 1H), 8.39 (d, 1H), 8.17 (d, 1H); ^{13}C NMR ($\text{DMSO-}d_6$) δ 189.14, 152.82, 137.86, 133.97, 127.06, 125.98, 125.00; ESI-MS: M-H^+ (m/z) 198.

3-Bromo-4-hydroxy-5-nitrobenzaldehyde (8): mp: 153 °C; ^1H NMR ($\text{DMSO-}d_6$) δ 9.82 (s, 1H), 8.42 (d, 1H), 8.28 (d, 1H); ^{13}C NMR ($\text{DMSO-}d_6$) δ 198.19, 153.59, 137.60, 137.15, 127.94, 126.70, 14.90; ESI-MS: M-H^+ (m/z) 245.

Picric acid (9): mp: 122 °C (reference¹⁷: 122 ~ 123 °C); ^1H NMR (CDCl_3) δ 8.724 (d, 2H); ^{13}C NMR (CDCl_3) δ 152.347, 138.082, 136.739, 125.257; ESI-MS: M-H^- (m/z) 228.

2-Chloro-4,6-dinitrophenol (10): mp: 112 °C; ^1H NMR ($\text{DMSO-}d_6$) δ 8.545 (d, 1H), 8.104 (d, 1H); ^{13}C NMR ($\text{DMSO-}d_6$) δ 162.611, 135.998, 129.150, 128.915, 126.973, 122.840; ESI-MS: M-H^+ (m/z) 217.

2-Bromo-4,6-dinitrophenol (11): mp: 120 °C; ^1H NMR ($\text{DMSO-}d_6$) δ 8.647 (d, 1H), 8.437 (d, 1H); ^{13}C NMR ($\text{DMSO-}d_6$) δ 152.362, 138.423, 135.806, 133.342, 120.123, 114.260; ESI-MS: M-H^+ (m/z) 261.

Preparation of 3-nitro-4-hydroxyphenylglycine. Nitric acid (4 mL) in diethyl ether (10 mL) was added a solution of 4-hydroxyphenylglycine (500 mg, 2.99 mmol) in diethyl ether (15 mL) at 0 °C and the reaction mixture was stirred for 1 hr. The precipitate was filtered, washed with diethyl ether and dried under vacuum to give a yellow solid (412 mg, 65%), mp 135 °C; ^1H NMR ($\text{DMSO-}d_6$) δ 8.01 (s, 1H), 7.62 (d, 1H), 7.18 (d, 1H), 5.20 (s, 1H); ^{13}C NMR ($\text{DMSO-}d_6$) δ 169.360, 152.638, 136.491, 134.868, 125.252, 124.023, 119.746; ESI-MS: M+H^+ (m/z) 213.

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References

- Olah, G. A.; Kuhn, S. J. *J. Am. Chem. Soc.* **1960**, *82*, 2380.
- Rieche, A.; Gross, H.; Höft, E. *Chem. Ber.* **1960**, *93*, 88.
- Youssefyeh, R. D. *Tetrahedron Lett.* **1964**, *32*, 2161.
- Tanaka, M.; Fujiwara, M.; Ando, H. *J. Org. Chem.* **1995**, *60*, 2106.
- Olah, G. A.; Laali, K.; Farooq, O. *J. Org. Chem.* **1985**, *50*, 1483.
- (a) Lee, D. G.; Spitzer, U. A. *J. Org. Chem.* **1970**, *35*, 3589. (b) Rao, Y. S.; Filler, R. *J. Org. Chem.* **1974**, *39*, 3589.
- Lou, J. D.; Lu, L. H.; Liu, W. *Synth. Commun.* **1997**, *27*, 3701.
- Khadilka, B.; Chitnavis, A.; Khare, A. *Synth. Commun.* **1996**, *26*.
- Einhorn, J.; Einhorn, C.; Ratajczak, F.; Pierre, J. L. *J. Org. Chem.* **1996**, *61*, 7452.
- (a) Markó, I. E.; Giles, P. R.; Tsukazaki, M.; Chellé-Regnaut, I.; Urch, C. J.; Brown, S. M. *J. Am. Chem. Soc.* **1997**, *119*, 12661. (b) Hinzen, B.; Lenz, R.; Ley, S. V. *Synthesis* **1998**, 977.
- Leanna, M. R.; Sowin, T. J.; Morton, H. E. *Tetrahedron Lett.* **1992**, *33*, 5029.
- (a) Jian, Z.; Wang, Z.; Wu, Y. *Huaxue Gongye Yu Gongcheng Jishu* **2005**, *26*(1), 5. (b) Jian, Z.; Wang, Z.; Wu, Y. *Jingxi Huagong Zhongqiantu* **2005**, *35*(1), 50. (c) Woodburn, H. M.; Lathroun, L. B. *J. Org. Chem.* **1954**, *19*, 285. (d) Engel, P.; Paradisi, F.; McCrohan, O.; Maguire, A.; Collins, S. G.; Busca, P.; Giacomini, D. Patent WO2006015885. (e) Chen, Y. T.; Seto, C. T. *J. Med. Chem.* **2002**, *45*, 3946. (f) Kanzaki, H.; Isobe, A.; Izumi, Y.; Yamada, H. *Agric. Biol. Chem.* **1990**, *54*(8), 2101. (g) Kondo, H.; Tanamachi, H.; Sunamoto, J. *Chem. Lett.* **1988**, *12*, 2013. (h) Garcia-Raso, A.; Deya, P. M.; Saa, J. M. *J. Org. Chem.* **1986**, *51*, 4285. (i) Park, J. K.; Jung, J. Y. *Enzyme. Microb. Tech.* **2002**, *30*(6), 726. (j) D'Auria,

- M.: Distefano, C.; D'Onofrio, F.; Mauriello, G.; Racioppi, R. *J. Chem. Soc. Perkin 1* **2000**, 20, 3513. (k) Craig, J. C.; Ekwuribe, N. N. *Synthesis* **1980**, 11, 909. (l) Cohen, T.; Song, I. H. *J. Am. Chem. Soc.* **1965**, 87(16), 3780. (m) Itoh, S.; Kato, N.; Ohshiro, Y.; Agawa, T. *Tetrahedron Lett.* **1984**, 25(42), 4753.
13. (a) Hendel, W.; Heu, F.; Poehlauer, P.; Winkler, B. U. S. Patent 2003045725. (b) Hendel, W.; Heu, F.; Poehlauer, P.; Winkler, B. U. S. Patent 2003144558.
14. Favier, I.; Dunach, E.; Hebrault, D.; Desmurs, J. R. *New J. Chem.* **2004**, 28, 62.
15. Herbst, R. M. *J. Am. Chem. Soc.* **1936**, 58, 2239.
16. March, J.; Smith, M. B. *MARCH'S Advanced Organic Chemistry*; Wiley: NY, 2001; p 696.
17. Budavari, S. *The Merck Index*, 17th Ed.; Merck & Co., Inc.: 1997.
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