An Efficient Carboxylation of 1-Naphthols using Magnesium Methyl Carbonate

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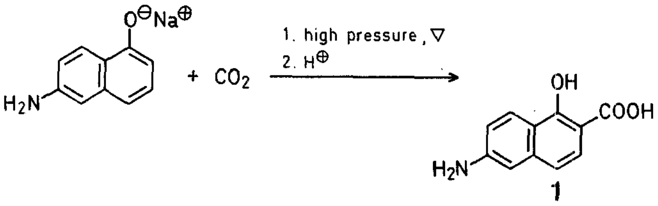
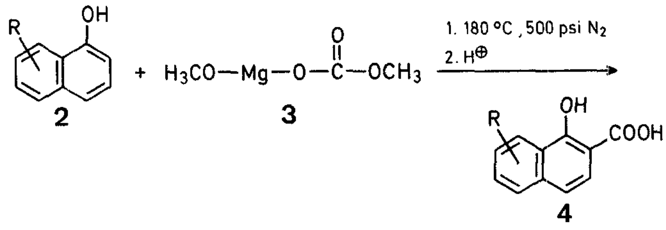
Our work required as a starting material 6-amino-1-hydroxy-2-naphthoic acid (**1**), which can be synthesized via the carboxylation of 6-amino-1-naphthol. Carboxylation of this naphthol is classically done by the Kolbe-Schmitt reaction using known literature procedures[1,2].



This method is normally quite satisfactory, but is adversely affected by many factors. A practical difficulty in carboxylating the naphthoxide is the maintenance of a strictly anhydrous, uniformly mixed, and finely divided solid state. If these conditions are not met, low yields, superheating and the subsequent byproducts often result. Another drawback of the method is the hard caking and charring that usually accompanies this reaction, causing difficult product isolation.

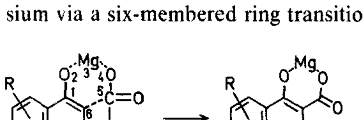
Since we were unable to efficiently prepare the necessary compound via the published Kolbe-Schmitt route, we looked for an alternate method. We now report that 1-naphthols **2** are carboxylated in high yield using magnesium methyl carbonate (**3**; *Stiles reagent*[3]) to give 1-hydroxy-2-naphthoic acids **4**.



The use of magnesium methyl carbonate (**3**) in carboxylation reactions that involve a magnesium chelated transition state is well documented[3,4]. However, there is only one report in the literature that describes the use of **3** in the carboxylation of hydroxy-arenes. These conditions succeeded only with highly reactive phenols such as resorcinol and in only 45% yield[5].

The conditions employed are similar to those for the Kolbe-Schmitt procedure: Pressures from 100 to 500 p.s.i. and temperatures from 135–180 °C. Some reactive 1-naphthols undergo the reaction with **3** at atmospheric pressure. However, unlike the Kolbe-Schmitt reaction where reactants are usually in the solid state, this reaction mixture is initially a homogeneous solution. Therefore, it does not suffer the lower yields due to inefficient mixing and caking. Work-up consists simply of treatment with dilute hydrochloric acid followed by filtration. The purity of the crude material obtained is generally acceptable for further synthetic elaboration. Examples of this reaction are shown in Table 1.

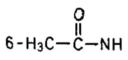
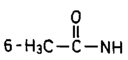
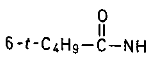
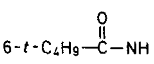
This reaction proceeds cleanly due to the chelating power of magnesium via a six-membered ring transition state.



Other hydroxy-arenes were subjected to the reaction conditions as shown in Table 2.

This reaction fails for phenol and proceeds for 2-naphthol only in the presence of added sodium methoxide. Also, resorcinol is bis-carboxylated in high yield to form exclusively 2,4-

Table 1. Reactions of Substituted 1-Naphthols **2** with Reagent **3**

Substrate 2 No.	R	Product 4 No.	R	Yield [%][a] by Method A[b]	Method B[c]	m.p. [°C] found	reported	Appearance[d]
2a	H	**4a**	H	96	23	186–188°	184–185°[7]	tan powder
2b	6-HO	**4b**	6-HO	100	100	220°	221°[8]	grey powder
2c	7-HO	**4c**	7-HO	100	100	217°	217°[9,10]	grey powder
2d	5-HO	**4d**	5-HO 6-HOOC	100	—	301-302°	300°[11]	yellow powder
2e	6-H_2N	**4e**	6-H_2N	84	—	200°	201°[1]	brown-black powder
2f	 $6\text{-}H_3C-\overset{O}{\overset{\|}{C}}-NH$	**4f**	 $6\text{-}H_3C-\overset{O}{\overset{\|}{C}}-NH$	80	6.5	213–215°	—[e]	tan powder
2g	 $6\text{-}t\text{-}C_4H_9-\overset{O}{\overset{\|}{C}}-NH$	**4g**	 $6\text{-}t\text{-}C_4H_9-\overset{O}{\overset{\|}{C}}-NH$	98	—	205–207°	—[e]	grey powder

[a] Not optimized yield of isolated product.

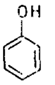
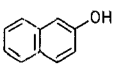
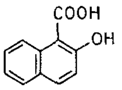
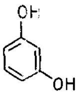
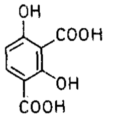
[b] 2 equivalents of reagent **3**, 500 p.s.i. nitrogen pressure, 180 °C, 6 h.

[c] Nitrogen, atmospheric pressure, 130 °C, 6 h.

[d] I.R., N.M.R., and mass spectra and microanalyses are consistent with the assigned structures. The purity is >90% as detected by N.M.R. and microanalyses.

[e] See experimental.

Table 2. Reaction of Hydroxyarenes with Reagent 3

Substrate	Product	Yield[a] [%]	m.p. [°C] found	m.p. [°C] reported	Appearance[b]
	—	$0^{c,d}$	—	—	—
		0^{c}; $21^{c,e}$	159–160°	156–157°[12]	white solid
		87^{c}	190°	179–181°[13]	tan solid

[a] Not optimized yield of isolated product.

[b] I.R., N.M.R., and mass spectra and microanalyses are consistent with the assigned structures. The purity is >90% as detected by N.M.R. and microanalyses.

[c] 2 equivalents of reagent 3, 500 p.s.i. nitrogen pressure, 180 °C, 6 h.

[d] Nitrogen, atmospheric pressure, 135 °C, 6 h.

[e] 1 equivalent of sodium methoxide added.

dihydroxyisophthalic acid by this method as opposed to the lower yield mixture of products obtained at atmospheric pressure[5].

1-Naphthol and 6-acetylamino-1-naphthol are carboxylated in only 21% and 6% yields, respectively, at atmospheric pressure. 1,5-Naphthalenediol is bis-carboxylated quantitatively to form 1,5-dihydroxy-2,6-naphthalenedicarboxylic acid using this new method, whereas, 1,6- and 1,7-naphthalenediols are only monocarboxylated in the expected 2-positions.

This new procedure offers an attractive alternative to the Kolbe-Schmitt reaction and its high yields and synthetic ease recommend it.

All reactions were conducted in a 300 ml stainless steel American Instruments Company micro-reaction vessel (bomb). Reagent 3 was prepared as a stock solution in dimethylformamide according to known literature procedures[4,6].

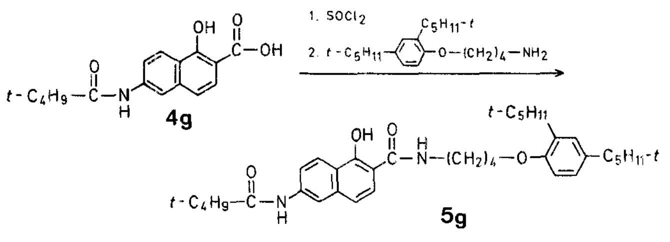
1-Hydroxy-2-naphthoic Acid (4a); Typical Procedure:

A solution of 1-naphthol (**2a**; 5.76 g, 0.04 mol) in a 1.8 molar dimethylformamide solution (40 ml) of reagent **3** (0.072 mol) is placed in a glass liner[14] in the reaction vessel. The vessel is pressurized to 500 p.s.i. (~34 atmospheres) with nitrogen and then heated at 180 °C for 6 h with no rocking. The vessel is allowed to cool to room temperature, the liner is removed, and the moist grey solids are scraped and washed out into an ice-water/dilute hydrochloric acid mixture (200 ml), *caution: foaming occurs*. This mixture is stirred for 1 h and filtered to give the product as a light tan solid which is of sufficient purity for further reactions; yield: 7.2 g (96%); m.p. 186–188 °C.

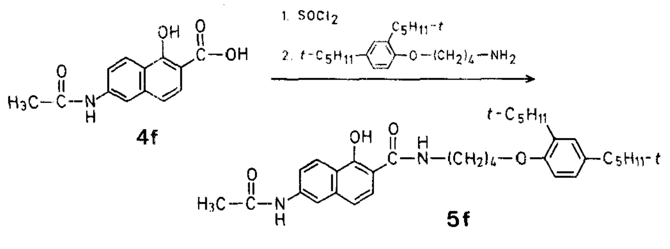
2-Hydroxy-1-naphthoic Acid:

A solution of 2-naphthol (5.76 g, 0.04 mol) and sodium methoxide (2.16 g, 0.04 mol) in a 1.8 molar dimethylformamide solution (40 ml) of reagent **3** (0.072 mol) is placed in the glass line in the reaction vessel. The vessel is pressurized to 500 p.s.i. with nitrogen and then heated at 180 °C for 6 h with no rocking. The vessel is allowed to cool to room temperature and the reaction mixture is drowned out into an ice-water/dilute hydrochloric acid mixture (200 ml), *caution: foaming occurs*. The oily product which separates is extracted with dichloromethane (2 × 20 ml). The extract is then extracted with saturated sodium hydrogen carbonate solution (4 × 50 ml) and the aqueous layer is acidified with 6 normal hydrochloric acid (80 ml). The precipitated white product is collected; yield: 1.6 g (21%); m.p. 159–160 °C.

Characterization of Products 4f and 4g:



4g → 5g



4f → 5f

The above reactions are performed using standard procedures: tetrahydrofuran as solvent, room temperature, 3 h.

Amide **5f**: yield: 80% (from crude **4f**); m.p. 180–181 °C.

$C_{33}H_{44}N_2O_4$	calc.	C 74.40	H 8.33	N 5.26
(532.7)	found	74.0	8.2	5.2

Amide **5g**: yield: 75% (from crude **4g**); m.p. 138–140 °C.

$C_{36}H_{50}N_2O_4$	calc.	C 75.22	H 8.77	N 4.87
(574.8)	found	75.0	8.7	4.6

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[1] *Swiss Patent* 257718 (1949), Ciba Ltd.; *C. A.* **44**, 6156 (1949).

[2] A. S. Lindsey, H. Jeskey, *Chem. Rev.* **57**, 583 (1957).

[3] H. L. Finkbeiner, M. Stiles, *J. Am. Chem. Soc.* **81**, 2598 (1959).

[4] H. L. Finkbeiner, M. Stiles, *J. Am. Chem. Soc.* **85**, 616 (1963).

[5] R. Mechoulam, Z. Ben-Zvi, *J. Chem. Soc. Chem. Commun.* **1969**, 343.

[6] Reagent 3 was also prepared as a stock solution in dimethyl sulfoxide and can be stored in standard brown bottles at room temperature for over a year without deterioration.

[7] *Dictionary of Organic Compounds*, Vol. 3, Oxford University Press, New York, 1965, p. 1750.

[8] H. Bader, S. January, *U.S. Patent* 3829443 (1974); *C. A.* **81**, 137598 (1974).

[9] Ref.[7], p. 1086.

[10] This reaction has also been carried out on a 50 g scale.

[11] H. Meyer, A. Hofmann, *Monatsh. Chem.* **38**, 141 (1917); *C. A.* **12**, 275 (1918).

[12] Ref.[7], p. 1749.

[13] Ref.[7], p. 1075.

[14] The use of a glass liner avoided difficult cleanup of the reaction vessel.