

Process Development for a Herbicide Intermediate via Catalytic Carboxylation of an Aromatic Diazonium Compound

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Abstract:

A laboratory process is described for the preparation of 2-sulfo-4-methoxybenzoic acid (SMBA) via diazotization of 2-amino-4-methoxy-sulfonic acid followed by Pd-catalyzed carbonylation in the presence of water. The most important process parameters were the catalyst precursor and water content. Both a two-step procedure using isolated diazonium compound as well as a one-pot reaction proved to be feasible. A yield of >95% SMBA was obtained after 3–4 h, using 1 mol % PdCl₂ at 8 bar and 60 °C. This is the first technically feasible catalytic carbonylation of an arene diazonium compound.

Background

2-Sulfo-4-methoxybenzoic acid (SMBA) is a key intermediate in the synthesis of CGA 308 956, a development herbicide of the former Ciba-Geigy AG (see Figure 1). Since the compound was not available commercially¹ and this specific substitution pattern is not easily accessible by the usual synthetic methods for *o*-sulfo benzoic acids such as gas-phase oxidation of the corresponding toluenesulfonic acid, a new and efficient synthesis had to be developed. The first kilograms for field trials and toxicological tests were prepared from 2,2'-disulfo-4,4'-dinitro stilbene, a dyestuff intermediate readily available within Ciba-Geigy. SMBA was obtained in the four-step synthesis depicted in Figure 2 via oxidation of the C=C bond and substitution of the nitro group in a nonoptimized overall yield of ca. 25%. However, it was obvious from the start that with an atom efficiency of 4.8%² this could not be a large-scale technical synthesis.

An alternative access to substituted benzoic acids would be the Pd-catalyzed carbonylation of aryl iodides and bromides as first described by Heck.³ However, besides the low catalyst activity, a major problem is the high cost of most aryl bromides, which in addition are often not available on large scale. The reports by Kikukawa et al.^{4,5} on the

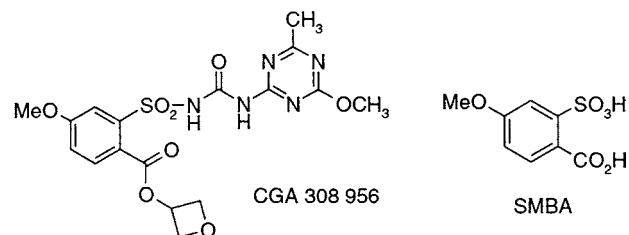


Figure 1. Structures of target compounds.

carbonylation of arene diazonium salts (see Figure 3) were therefore of high interest to us. Since 2-amino-4-methoxy-sulfonic acid was commercially available at reasonable cost, a feasibility study was started. This note describes our efforts to develop a technically feasible catalytic process for the large-scale preparation of SMBA.

Feasibility Study. First experiments were carried out with the isolated diazonium salt prepared by diazotization of 2-amino-4-methoxy-sulfonic acid under classical conditions (H₂O, HCl, NaNO₂) which readily precipitated from the reaction solution.⁶ This inner salt is surprisingly stable, and according to DSC decomposes only at temperatures >160 °C. The original reactions conditions described by the Kikukawa team (acetonitrile, NaOAc, 2 mol % Pd(OAc)₂) were, in principle, successful, but several modifications proved to be beneficial to our system. Sodium acetate was replaced by water as nucleophile (ca. 2% in acetonitrile, ca. 2 equiv/diazonium compound), and the catalyst was added just before the reaction in the presence of CO to get reproducible results. In addition, a reliable analytical method had to be developed which in our experience is often difficult for highly water-soluble compounds. Yields of SMBA as determined by HPLC in the reaction solution were >80%, but a rather long reaction time of 20 h was needed for good conversions.

Process Optimization. Catalyst costs are certainly an issue since rather high catalyst loadings are necessary. Because palladium acetate is very expensive, several other Pd precursors were tested. Fortunately, commercially avail-

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- (1) SMBA (CAS 40567-33-7) is only described in the patent literature, Koike, W.; Kimoto, T.; Matsui, S. (Ihara Chemicals). DE 2616611, 1977. Purified samples melted at 122 °C (sintering between 90 and 100 °C); ¹H NMR (DMSO, 250 MHz) 3.94 ppm (s, 3H), 7.16 ppm (m, 1H), 7.47 ppm (m, 1H), 7.93 ppm (m, 1H).
- (2) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259.
- (3) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: London, 1985.
- (4) Kikukawa, K.; Kono, K.; Nagira, K.; Wada, F.; Matsuda, T. *Tetrahedron Lett.* **1980**, *21*, 2877. Kikukawa, K.; Nagira, K.; Wada, F.; Matsuda, T. *J. Org. Chem.* **1980**, *45*, 2365. Kikukawa, K.; Kono, K.; Nagira, K.; Wada, F.; Matsuda, T. *J. Org. Chem.* **1981**, *46*, 4413.

- (5) For a recent overview, see: Beller, M. In *Applied Homogeneous Catalysis by Organometallic Complexes*, 2nd ed.; Cornils, B., Herrmann, W. A., Eds.; Wiley-VCH: Weinheim, 2002; p 145.
- (6) Experimental procedure for the diazotization: 48 g of 2-amino-4-methoxy-sulfonic acid were suspended in 100 mL of water and 100 mL of 37% hydrochloric acid and cooled to 10 °C. Sodium nitrite (10.4 g, dissolved in 10 mL water) was added within 2 h under stirring, and the reaction mass was stirred for an additional 1 h; 5.6 g of sulfamic acid was then added. The precipitated product was filtered and washed with 20 mL of 2 N HCl, methanol, and diethyl ether, respectively. The light yellow crystals were dried at rt; yield: 98%.

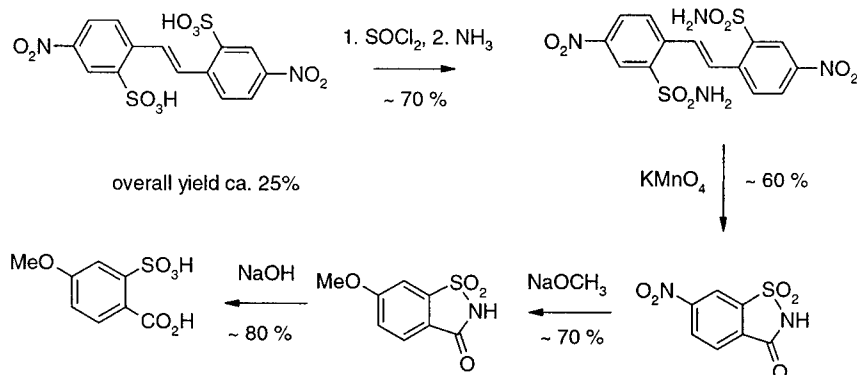


Figure 2. Kilogram-scale synthesis starting from dyestuff intermediate.

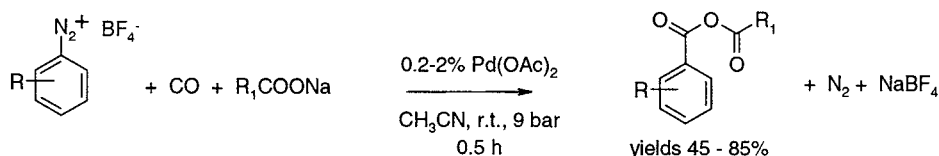


Figure 3. Typical conditions for the preparation of mixed anhydrides from diazonium salts.

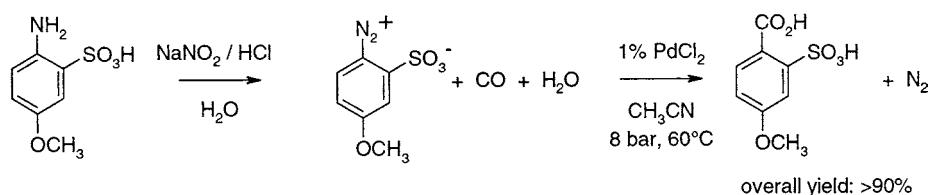


Figure 4. Laboratory process for the production of SMBA.

able solid PdCl₂ proved to be just as effective, whereas the cheaper PdCl₂ solutions or Pd–dibenzylideneacetone complexes gave significantly lower selectivities or yields or both.

First experiments showed that the palladium can be separated from the reaction solution and recovered by adding active carbon followed by mild reduction by hydrogen.⁷ Recovery of Pd was >95%, but under these nonoptimized conditions, some acetonitrile was hydrogenated which can lead to problems in the next reaction step. This aspect was not investigated further.

Since acetonitrile was confirmed to be the solvent of choice, solvent effects were studied only within narrow limits. The reaction could be run in water but yields dropped to 40%; in the absence of water, formation of the anhydride could be expected (which would be an advantage for the next reaction step), but the reaction stopped after about 20% conversion. In the end, the optimal amount of water was 5–15 equiv relative to the amount for the diazonium intermediate. Using 1 mol % PdCl₂ under an initial CO pressure of 8 bar (venting the gas phase 2–3 times to remove the nitrogen) at 60 °C gave >95% of SMBA (HPLC) within 6 h (see Figure 4).

Towards a Pilot Process. In this development phase the following aspects were investigated: removal of nitrogen on a larger scale, optimization of the reaction variables such as concentration of starting material, water content, and so on, suitability of the product for the next reaction step, and safety aspects.

Table 1: Optimized reaction conditions for the synthesis of SMBA⁸

concentration of diazonium compound	20% w/w in acetonitrile
PdCl ₂	1 mol % (s/c 100)
water content	14 equiv/diazonium compd
<i>p</i> (CO), <i>T</i>	8 bar (variant 2), 60 °C
reaction time	3–4 h
active carbon (0.1 bar H ₂ , rt)	4 g/mol diazonium compd, reaction time 2 h
isolated yield (content in solid)	>95% (ca. 85%, H ₂ O, byproducts)
recovered Pd on active carbon	85–95%

With the help of a heat-flow calorimeter to get information on the course of the very exothermic reaction (ca. 330 kJ/mol), two variants were studied for the removal of N₂: (1) Continuous dosage of CO via a massflow controller combined with the slow release of a mixture of N₂ and CO (total pressure 8 bar). (2) Stepwise reaction by pressurizing to 8 bar CO, waiting for all CO to react (ca. 45 min), releasing the nitrogen, and repeating the procedure four times. Both procedures gave similar maximum heat flows and yields; in variant 1 about 20–40% excess of CO was needed.

(8) Experimental procedure using isolated diazonium intermediate: 100 g of dry diazonium compound together with 277 g of acetonitrile and 55.8 g of water were placed in an 850-mL glass autoclave. The reactor was flushed three times with 8 bar argon. PdCl₂ (0.83 g dissolved in 17 g of acetonitrile) was added and the reactor immediately pressurized to 8 bar CO. The reaction mixture was heated to 60 °C; after 30 min the autoclave was vented to 3 bar and the pressure increased again to 8 bar with CO; this cycle was repeated five times. After 3 h the pressure was completely released. After evaporation the light-brown 2-sulfo-4-methoxybenzoic acid was dried at 60 °C: yield 97%.

(7) For a precedent, see: Baumeister, P.; Meyer, W.; Oertle, K.; Seifert, G.; Siegrist, U.; Steiner, H. *Chimia* **1997**, *51*, 144.

We also investigated the possibility to carry out the reaction without isolating the diazonium intermediate. A “one-pot” procedure would, of course, be a real advantage and would give considerable cost savings. A major problem is the oxidizing character of NaNO_2 which would interfere with the Pd^0 species assumed to insert into the $\text{C}-\text{N}_2^+$ bond via an oxidative addition as a first step of the accepted catalytic cycle of the carbonylation reaction.⁵ For this reason the excess of nitrite was destroyed after the diazotization with sulfamic acid; acetonitrile and PdCl_2 were then added to the reaction solution, and the reaction was started by pressuring with CO . To our pleasant surprise, after a reaction time of 6 h we could obtain assay yields of SMBA up to 88%.

Summary and Conclusions

The optimal process conditions are summarized in Table 1. Compared to the original procedure described by Kiku-

kawa et al., the replacement of NaOAc by water, the water concentration, the use of PdCl_2 as catalyst, and working at $60\text{ }^\circ\text{C}$ had the most beneficial effect on yield and reaction rate. The carbonylation route has an atom efficiency of 55%, and to our knowledge it is the first technically feasible catalytic carbonylation of an arene diazonium compound. We have indications that the procedure is quite general for the synthesis of 2-sulfo benzoic acids.

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