A Convenient Synthesis of 2-Ethyl-6-(1-hydroxyethyl)aniline—An Alachlor Metabolite Synthon

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Application of the Sugasawa method to the synthesis of 2-ethyl-6-(1-hydroxyethyl)aniline, an alachlor metabolite precursor, was demonstrated to yield the desired product in high yield without contamination with other isomers in two easy steps from commercially available reagents.

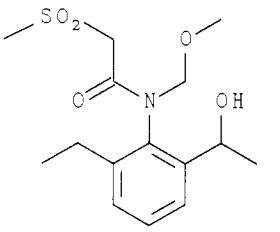
INTRODUCTION

Alachlor, 2-chloro-*N*-(2,6-diethylphenyl)-*N*-(methoxymethyl)acetamide, is one of the most widely used herbicides in North America. In plants, it is metabolized principally to two products, the major one of which is the hydroxylated sulfone IV (Figure 1) (Sharp, 1988). Trace analysis of alachlor residues in food products requires both metabolite IV and its hydrolysis product, 2-ethyl-6-(1-hydroxyethyl)aniline (III), as reference analytical standards (Cowell et al., 1987). In the past, these compounds have been available from the EPA Chemical Standard Repository, but recently adopted economies have made them less accessible. In anticipation of further work with the alachlor metabolites, consideration was given to synthesis of compound III for use both as an analytical standard and as a synthetic intermediate for metabolite IV.

There is one published synthesis of III (Wratten et al., 1987) in which an indole ring is first constructed from 2-ethylaniline (I) to ensure ortho-specificity. The indole is purified by vacuum distillation prior to subsequent reactions. Although this is an elegant approach, it requires four steps with an overall yield of 49%. Consideration, therefore, was given to alternative ways of specifically acylating the readily available 2-ethylaniline (I) at the ortho-position. The Friedel–Crafts and photo-Fries reactions were rejected because of nonspecificity. Metalation of various aniline derivatives is specific to the ortho-position (Muchowski et al., 1980; Fuhrer and Gschwend, 1979), but in toluidine derivatives, competing metalation has been observed at the methyl group so this approach was also rejected (Fuhrer and Gschwend, 1979; Katritzky et al., 1990). The azasulfonium method (Gassman and Gruetzmacher, 1973) specifically alkylates toluidine at the ortho-position, but the yield was low and further reactions would have been necessary to convert the initially formed sulfide into the carbonyl function. The most promising approach seemed to be that of Sugasawa et al. (1978) in which boron trichloride directs a nitrile to react specifically at the ortho-position of an aniline (see Figure 2). Although the reaction had not been demonstrated with 2-alkylanilines, its simplicity was appealing. The purpose of this paper is to convey the results of this approach.

MATERIALS AND METHODS

Chemicals and Supplies. 2-Ethylaniline (I), distilled prior to use (97–98 °C at 20 mmHg), aluminum trichloride, and boron trichloride, 1 M in heptane, were purchased from Aldrich Chemical Co. Solvents were distilled-in-glass grade (Caledon Labs, Georgetown, ON). Thin-layer plates were Whatman MK6F silica, 250 μm, 1 in. × 3 in. (Chromatographic Supplies, Brockville, ON). Nitrogen was prepurified grade (Linde). Silica gel, grade 643, 200–425 mesh, was purchased from Aldrich for flash chromatography. Sodium borohydride was purchased from BDH Chemicals, Toronto, ON.



IV

Figure 1. Alachlor metabolite IV.

Instrumentation. ^{1}H NMR spectra were run on a Bruker 200-MHz instrument at 22 °C in $CDCl_3$ referenced to the $CHCl_3$ signal at 7.26 ppm, and mass spectra were recorded on a VG Analytical ZAB 2F instrument in low resolution using a direct inlet probe and electron impact mode at 70 eV.

2-Amino-3-ethylacetophenone (II). An oven-dried, two-necked, round-bottom flask (500 mL) equipped with a condenser, a dropping funnel, and a Teflon-coated magnetic stirring bar was cooled under nitrogen in a fumehood. A 1 M heptane solution of boron trichloride (20 mL, 20 mmol) was transferred to the flask by pipet, and the flask and contents were chilled in an ice bath. A solution of 2-ethylaniline (I) (2.1 g, 17.4 mmol) in toluene (15 mL) was then added dropwise over 10–15 min (approximately 1–2 drops/s) with stirring. A milky, white suspension formed. An additional 5 mL of toluene was used to rinse the funnel. The reaction mixture was stirred for 5 min, and then acetonitrile (2.9 mL, 52 mmol) was added rapidly followed within 2–3 min by aluminum trichloride (2.3 g, 19 mmol). The funnel was replaced with a glass stopper. The reaction mixture was stirred for a further 10 min at ice temperature, the ice bath removed, and stirring continued for 20 min. During this period, the solids dissolved and a second, pale yellow liquid phase was produced. The reaction mixture was then gently refluxed with stirring overnight (22 h) under a nitrogen blanket.

Hydrolysis of the intermediate ketimine was effected by adding 30 mL of 1 N sulfuric acid (**CAUTION**: extremely exothermic, add dropwise very slowly initially!) and refluxing for 1 h. The reaction mixture was cooled to room temperature and transferred to a separatory funnel with 25 mL of water and 25 mL of hexane. The organic layer was separated and washed with 20 mL of water and then with 10 mL of neutral phosphate buffer saturated with brine. After drying over anhydrous sodium sulfate and filtering, the organic layer was concentrated under reduced pressure and traces of solvent were removed by high vacuum to yield a light amber syrup (1.8 g, 64%) which crystallized on standing in the refrigerator, mp 38–40 °C. Thin-layer chromatography (10% EtOAc in hexane) showed a single spot II (R_f 0.35) which quenched UV at short wavelength, fluoresced at long wavelength, and slowly

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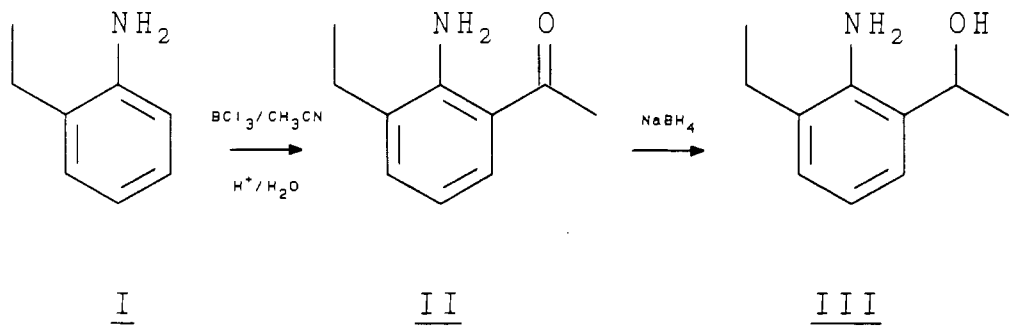

Figure 2. Synthetic scheme for preparing 2-ethyl-6-(1-hydroxyethyl)aniline (III).

charred blue-black on heating after spraying with phosphomolybdic acid. The starting aniline I, R_f 0.26, which does not fluoresce at long wavelength and rapidly chars brown under the same conditions, was not evident. ^{1}H NMR ($CDCl_3$) δ 7.64 (d, 1 H), 7.22 (d, 1 H), 6.64 (t, 1 H), 6.5 (brd), 2.60 (s, 3 H), 2.51 (q, 2 H), 1.27 (t, 3 H); MS (m/z, rel intensity): 163, 60%, M^+; 148, 100%, $M^+ - CH_3$; 120, 5%, $M^+ - CH_3CO$. A portion was recrystallized from hexane, mp 41–42 °C [lit. mp 40–41 °C (Wratten et al., 1987)].

The acidic aqueous layer was made basic with 10 M NaOH (20 mL) and extracted with methylene chloride (2 × 20 mL). The combined extracts were dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to yield 0.56 g of amber liquid with a strong odor of 2-ethylaniline (I). The ratio of product II and aniline I in this fraction was 62:38 by NMR.

2-Ethyl-6-(1-hydroxyethyl)aniline (III). Sodium borohydride (150 mg) was added at once to a stirred methanolic (10 mL) solution of crude acetophenone II (1.1 g, 6.7 mmol) in a 50-mL round-bottom flask at room temperature; effervescence was vigorous. After 15 min, a further portion of borohydride was added (100 mg) and the reaction stirred for a further 30 min. The bulk of the methanol was removed under reduced pressure, and the residue was mixed with 10 mL 1 N NaOH and 10 mL of methylene chloride. The organic layer was removed in a separatory funnel and the flask rinsed with 10 mL of methylene chloride, which was then used to extract the aqueous layer again. This was repeated a second time. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The product was a light amber syrup (1.05 g, 94%) which solidified within minutes at room temperature, mp 58–60 °C. A portion was recrystallized from 5% EtOAc–hexane, mp 64.5–65 °C [lit. mp 60–61 °C (Wratten et al., 1987)]. Thin-layer chromatography of the crude product (30% EtOAc–hexane) showed a single, major spot III at R_f 0.34 and two traces at R_f 0.63 (possibly I) and R_f 0.54. A portion of the product (0.84 g) was purified by flash chromatography on silica with 25% EtOAc–hexane (yield, 0.78 g). ^{1}H NMR ($CDCl_3$) δ 7.04 (d, 1 H), 6.99 (d, 1 H), 6.72 (t, 1 H), 4.96 (q, 1 H), 3.4 (brd, 3 H, D_2O exchanged), 2.54 (q, 2 H), 1.61 (d, 3 H), 1.27 (t, 3 H); MS (m/z, rel intensity) 165, 4%, M^+; 147, 80%, $M^+ - H_2O$; 132, 100%; 117, 40%.

RESULTS AND DISCUSSION

2-Amino-3-ethylacetophenone (II) is a very weak base, presumably as a result of intramolecular hydrogen bonding between the amino protons and the carbonyl group. As a result, 84% of the product of the Sugasawa reaction was found in the "neutral" organic layer on workup and was sufficiently pure (≥95% by NMR) to be used in the next step without further purification. The unreacted starting aniline I and the minor impurities are more basic and were found in the aqueous acid layer with the remaining 16% of the product II.

The borohydride reduction step was quantitative, and the product III was readily purified by either recrystallization or flash chromatography (Still et al., 1978). If the acetophenone II was recovered from the aqueous acid layer of the first reaction and included in the reduction, the overall yield of the product III was ≥75% in two steps from commercially available starting materials. There was no evidence in the NMR spectrum of a para-substituted product.

Sugasawa et al. (1978) found that the choice of solvent had no effect on yield, and that observation was corroborated in this work. The yield was identical when 1,2-dichloroethane was substituted for toluene but fell by 20% when 2-ethylaniline (I) was added neat. When 2-ethylaniline (I) was added dropwise in solvent, a fine dispersion of the amine–borane complex was formed, but when added neat, it tended to aggregate and made mixing more difficult. Sugasawa et al. (1978) also noted that addition of aluminum chloride gave a higher yield. Although its role in the reaction is not clear, the yield fell to 32% when it was not used.

Distillation of the 2-ethylaniline (I) was not necessary with respect to yield, but did remove a contaminant that was evident on TLC just ahead of product II and which passed through both stages unchanged.

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