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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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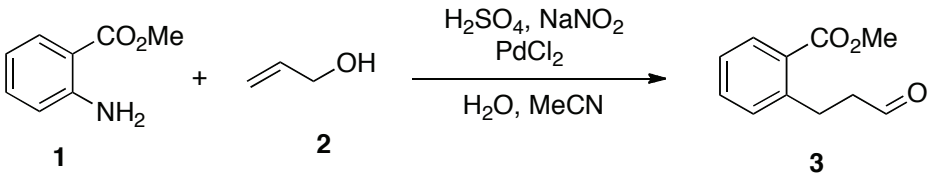
ONE-POT DIAZOTIZATION AND HECK REACTION OF METHYL ANTHRANILATE: 2-(3-OXOPROPYL)BENZOIC ACID METHYL ESTER



1 2 3

Submitted by Florencio Zaragoza.[1]
Checked by Fumiki Kawagishi and Tohru Fukuyama.

1. Procedure

2-(3-Oxopropyl)benzoic acid methyl ester (**3**). To a 1-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar (round, 9 x 50 mm) and an internal thermometer are added methyl anthranilate (15.1 g, 0.100 mol, 1.00 equiv) (Note 1), MeCN (150 mL) and a mixture of sulfuric acid (11.3 mL, 20.7 g, 0.210 mol, 2.10 equiv) and water (100 mL) at room temperature. Allyl alcohol (12.8 g, 0.220 mol, 2.20 equiv) and a solution of $PdCl_2$ (112 mg, 0.630 mmol, 0.00630 equiv) in MeCN (50 mL) (Note 2) are then added. Finally, while stirring vigorously, a solution of $NaNO_2$ (8.48 g, 0.123 mol, 1.23 equiv) in water (20 mL) is added in one portion (Note 3). After an induction period of 0.5 h to 2 h, a slightly exothermic reaction ensues. The temperature of the mixture is kept below 40 °C by cooling with a water bath (Note 4).

The mixture is stirred at room temperature for 8 h, diluted with water (0.5 L), and extracted (3 × 50 mL EtOAc). The combined organic extracts are washed once with brine (135 g), dried over $MgSO_4$ (25 g) for 15 min, filtered, and concentrated under reduced pressure (final pressure/temperature: 20 mmHg, 35 °C) to yield 18.67 g of an oil (Note 5). Short path vacuum distillation (30 mmHg, 105 °C) of this oil yielded 11.73 g (61.0%) of the title aldehyde as slightly yellow oil (Note 6).

2. Notes

1. The submitter purchased methyl anthranilate (> 98.0%), allyl alcohol (> 98.0%), $PdCl_2$ (anhydrous, 60% Pd), and $NaNO_2$ (> 98.0%) from

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Fluka, MeCN (> 99.0%) and H_2SO_4 (95-97%) from Merck KGaA. The checkers purchased methyl anthranilate (99+%) from Aldrich Chemical Co., allyl alcohol (> 99%) from Tokyo Chemical Industry Co., $PdCl_2$ (anhydrous, 60% Pd) from Fluka, $NaNO_2$ (> 98.5%) from Kanto Chemical Co., MeCN (> 99.0%) and H_2SO_4 (> 95.0%) from Wako Pure Chemical Industries respectively. No inert atmosphere is required.

2. This solution is prepared by stirring $PdCl_2$ and MeCN at 80 °C for 18 h. No undissolved $PdCl_2$ should remain visible.

3. During the addition of $NaNO_2$ the mixture turns red but finally a yellow-orange solution should result. The diazotization leads to an immediate temperature increase to approximately 40 °C, which wears off within 15–30 min, depending on the scale of the preparation. Two liquid phases are usually formed, and a gentle gas evolution takes place.

4. Unsurprisingly, the larger the scale, the more pronounced the exotherm. Cooling becomes usually necessary when more than 50 g of methyl anthranilate are employed. The current procedure has been performed successfully with up to 60 g (0.4 mol) of methyl anthranilate. When the exotherm ceases and the reaction mixture reaches room temperature no more product is formed.

5. According to the submitter, this oil contains approximately 62% (weight) of the title compound based on ^{1}H NMR with an internal standard (4-nitrobenzaldehyde). The crude product may contain variable amounts of the corresp onding hydrate (2-(3,3-dihydroxypropyl)benzoic acid methyl ester): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.02 (m, 2 H), 3.08 (br t, J = 7 Hz, 2 H), 4.89 (t, J = 6 Hz, 1 H), 7.28 (m, 2 H), 7.45 (t, J = 7 Hz, 1 H), 7.89 (d, J = 7 Hz, 1 H). The EtOAc-extract may be used directly for ensuing synthetic operations. Thus, treatment of this extract with $NaBH_4$, followed by saponification, yielded 2-(3-hydroxypropyl)benzoic acid in 53% overall yield (three steps). Analytical data were as follows: Mp (toluene) 68–69 °C (lit.[2] Mp (benzene) 70 °C); ^{1}H NMR (300 MHz, d_6-DMSO) δ: 1.68 (quintet, J = 7 Hz, 2 H), 2.91 (t, J = 7 Hz, 2 H), 3.39 (t, J = 6 Hz, 2 H), 4.45 (s, br, 1 H), 7.28 (m, 2 H), 7.43 (d, J = 7 Hz, 1 H), 7.73 (d, J = 7 Hz, 1 Hz, 1 H), 12.80 (br s, 1 H).

6. A small forerun, mainly methyl benzoate, was collected and discarded. Analytical data: IR (film): 2952, 1720, 1435, 1259, 1087 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.81 (td, J = 7.8, 1.4 Hz, 2 H), 3.28 (t, J = 7.8 Hz, 2 H), 3.90 (s, 3 H), 7.26-7.31 (m, 2 H), 7.44 (td, J = 7.8, 1.4 Hz, 1 H), 7.93 (dd, J = 7.8, 1.4 Hz, 1 H), 9.82 (t, J = 1.4 Hz, 1 H); ^{13}C NMR (100

MHz, $CDCl_3$) δ: 27.3, 45.5, 52.0, 126.5, 129.2, 131.0, 131.2, 132.4, 142.6, 167.6, 201.7; Anal. calcd. for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29; found: C, 68.58; H, 6.28. The product may undergo aldol addition and condensation upon prolonged storage. According to the submitter, ^1H NMR with an internal standard (4-nitrobenzaldehyde) indicated that the distilled product contained 96% (weight) of the title compound. The purity of the product was 97% by GC analysis. Anal. calcd. for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29; found: C, 68.58; H, 6.28.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Aryldiazonium salts are cheap, readily accessible intermediates for Pd-catalyzed C-C bond forming reactions.[3] Because aryldiazonium salts are potentially explosive and often carcinogenic, one-pot procedures, which obviate the isolation of these salts, are more convenient than procedures based on isolated diazonium salts,[4] and may even be applicable to large-scale preparations.

3-Arylpropanals are useful synthetic intermediates, and are widely used as fragrances in cosmetics, perfumes, and numerous household products. The present procedure offers a practical one-step conversion of anilines into 3-arylpropanals. It is based on readily available reagents, requires only 0.5-1.0% of $PdCl_2$, and does without anhydrous solvents or heating or cooling. Other allylic alcohols than allyl alcohol, such as 3-buten-2-ol, can also be used in the present procedure, to yield the corresponding 1-aryl-3-butanones. Particularly well suited for this protocol are anilines ortho-substituted with electron-withdrawing groups (alkoxycarbonyl, cyano, acetyl, trifluoromethyl, halogens). Ortho-unsubstituted anilines yield mixtures of 3-arylpropanals and 2-arylpropanals, which can, however, be separated by bisulfite adduct formation.[5]

Although diazotizations are often performed with only one equivalent of nitrite, in the present procedure an excess of nitrite actually results in higher yields and clean crude products. Thus, if the title procedure is

performed with only 1.0 equivalent of sodium nitrite, a product mixture containing only small amounts of the desired aldehyde is obtained. Although alcohols readily react with HNO_2 to yield alkylnitrites, this potential side reaction appears not to interfere with the diazotization or the Heck reaction.
2-(3-Oxopropyl)benzoates have previously been prepared by oxidative cleavage of tetralones[6] and by oxidation of 2-(3-hydroxypropyl)benzoates.[7]

1. Lonza AG, CH-3930 Visp, Switzerland; florencio.zaragoza@lonza.com. I gladly acknowledge the skillful technical assistance by Verena Heinze and the GC-analysis by Simon Gaul.

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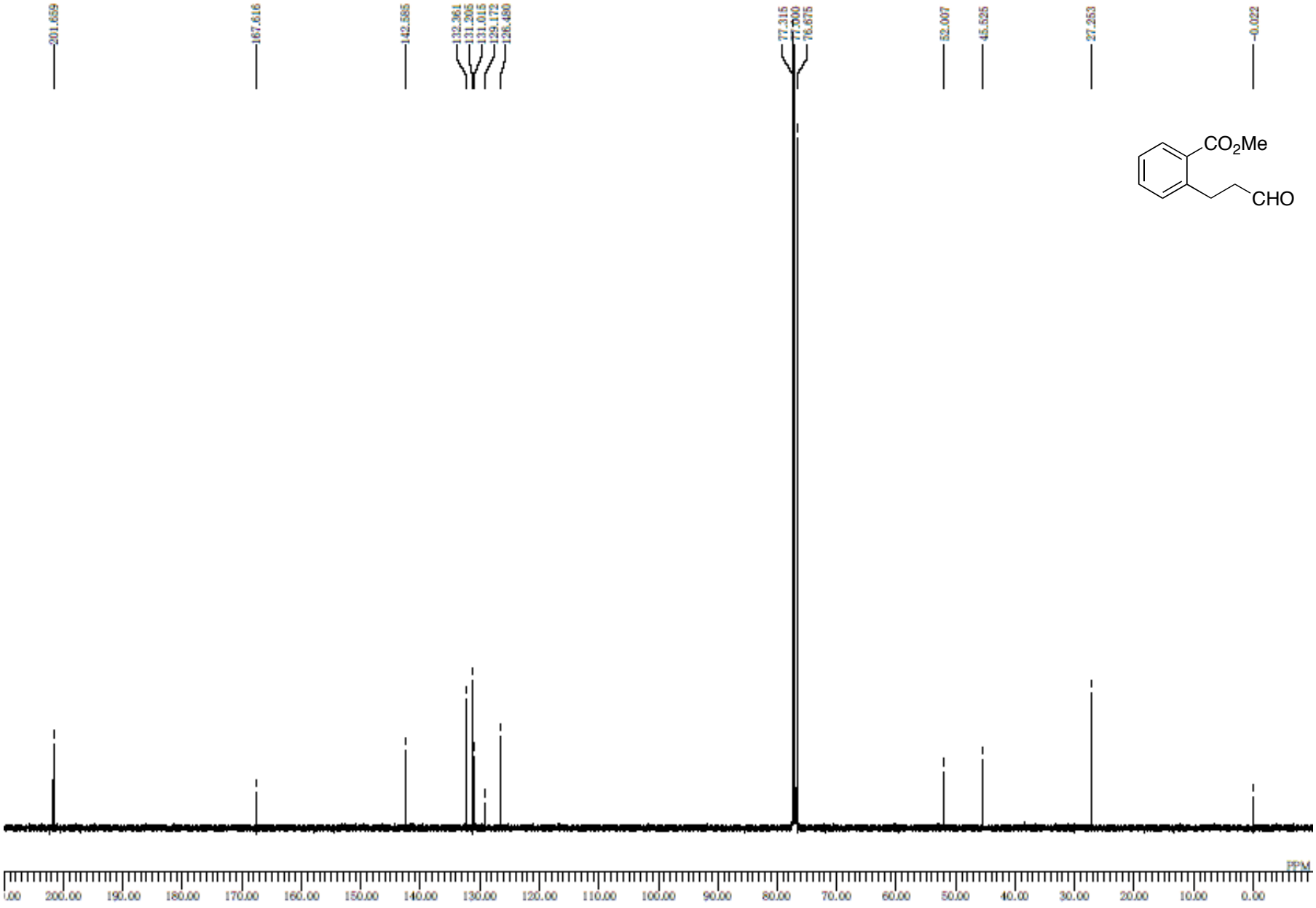
Appendix
Chemical Abstracts Nomenclature; (Registry Number)

Methyl anthranilate; (134-20-3)
Allyl alcohol; (107-18-6)
Methyl 2-(3-oxopropyl)benzoate; (106515-77-9)

Florencio Zaragoza was born 1964 in Hamburg (Germany). He studied chemistry in Göttingen (Germany), and obtained his doctorate 1990 under the guidance of Professor Franck-Neumann in Strasbourg (France). After postdoctoral training with Professor Pfaltz in Basel (Switzerland) and Professor A. P. Marchand in Denton (TX, USA) he initiated his habilitation in Dresden (Germany). From 1994 until 2007 he worked as medicinal chemist at Novo Nordisk A/S (Måløv, Denmark), and since 2007 as process development chemist at Lonza AG in Switzerland.

Fumiki Kawagishi was born in 1986 in Shizuoka, Japan and received B.S. in 2009 from the University of Tokyo. In 2009 he began his graduate studies at the Graduate School of Pharmaceutical Sciences, the University of Tokyo, under the guidance of Professor Tohru Fukuyama. His research interests are in the area of total synthesis of natural products.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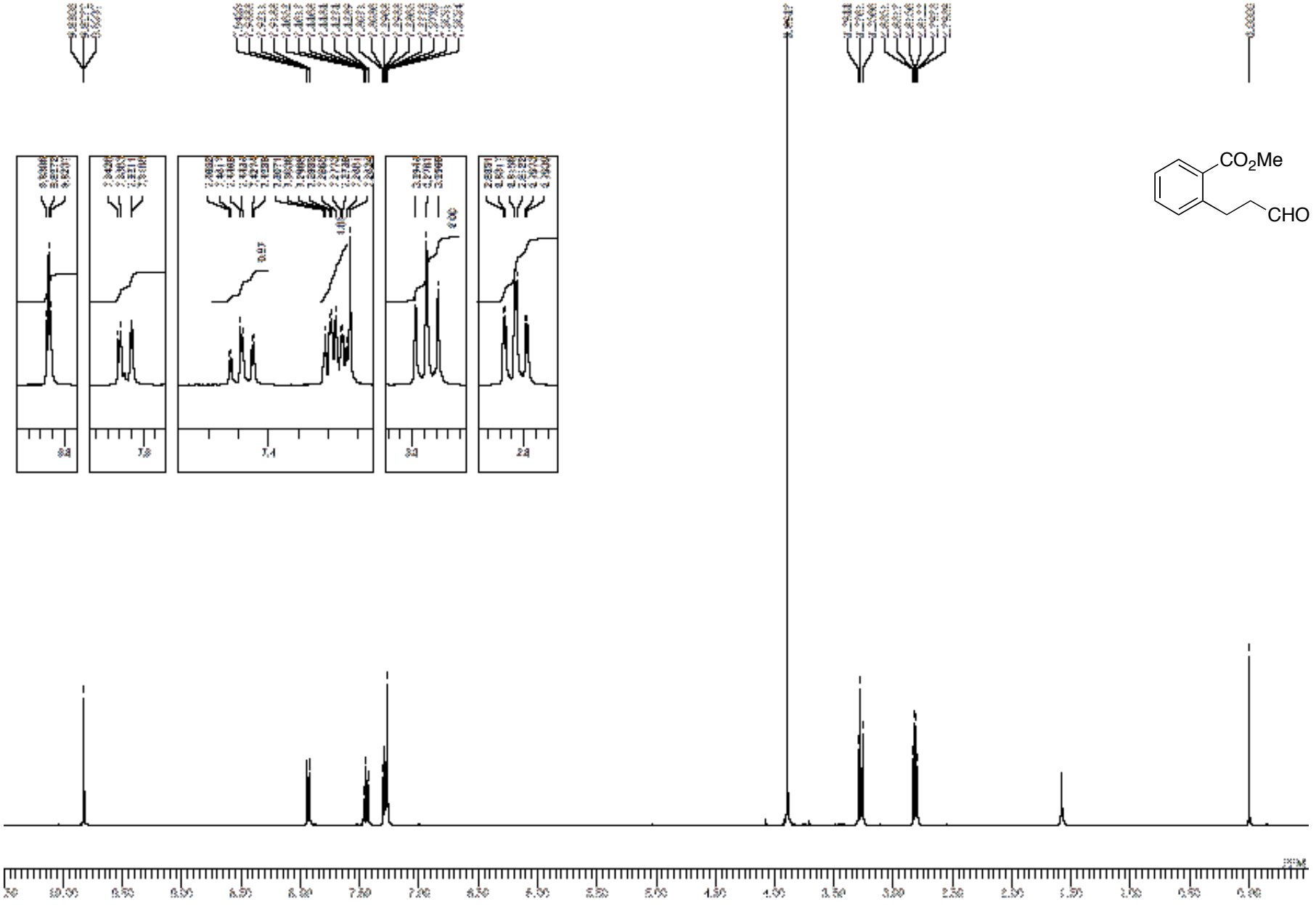
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