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of Reliable Methods
for the Preparation
of Organic Compounds

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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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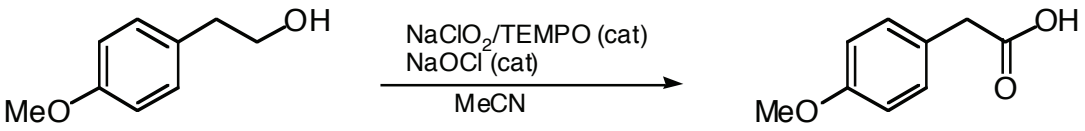
OXIDATION OF PRIMARY ALCOHOLS TO CARBOXYLIC ACIDS WITH SODIUM CHLORITE CATALYZED BY TEMPO AND BLEACH: 4-METHOXYPHENYLACETIC ACID
(Benzeneacetic acid, 4-methoxy-)



1f **2f**

Submitted by Matthew M. Zhao,[1] Jing Li,[1] Eiichi Mano,[2] Zhiguo J. Song,[1] and David M. Tschaen.[1]
Checked by Arun Ghosh, Jamie Sieser, Weiling Cai, and Sarah E. Kelly.

1. Procedure

A. 1-L, three-necked, round-bottomed flask equipped with a mechanical stirrer and two 100-mL addition funnels is charged with 4-methoxyphenethyl alcohol (**1f**) (6.09 g, 40 mmol), TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy free radical) (0.436 g, 2.8 mmol), 200 mL of acetonitrile, and 150 mL of 0.67M sodium phosphate buffer (pH 6.7) (Notes 1,2). A solution of sodium chlorite is prepared by dissolving 80% $NaClO_2$ (9.14 g, 80.0 mmol) in 40 mL of water and a solution of dilute sodium hypochlorite (NaOCl) is prepared by diluting household bleach (5.25% NaOCl, 1.06 mL, ca. 2.0 mol%) with 19 mL of water. The reaction mixture is heated to 35 °C with stirring and approximately 20% of the $NaClO_2$ solution is added via one addition funnel followed by 20% of the dilute bleach solution via the other funnel. The remaining portions of both reagents are then added simultaneously over 2 h (Note 3). The resulting mixture is stirred at 35 °C until the reaction is complete (Note 4) (usually 6-10 h). After cooling the reaction mixture to 25 °C, 300 mL of water is added and the pH is adjusted to 8.0 by addition of ca. 48 mL of 2.0N NaOH. The reaction mixture is then poured into ice-cold sodium sulfite solution (12.2 g in 200 mL of water) maintained below 20 °C with an ice-water bath (Note 5). After stirring for 0.5 h at rt, 200 mL of methyl t-butyl ether (MTBE) is added and the resulting mixture is stirred for 15 min. The

organic layer is separated and discarded. More MTBE (100 mL) is added and the rapidly stirred mixture is acidified with 2.0N HCl to pH 3-4. The organic layer is separated and the aqueous layer is extracted with two 100-mL portions of MTBE. The combined organic phases are washed with two 100-mL portions of water, 100 mL of brine, and then concentrated to give 6.16-6.22 g (93-94%) of 4-methoxyphenylacetic acid (**2f**) as a colorless solid (Note 6).

2. Notes

1. All reactants and reagents were obtained from Sigma-Aldrich and used without purification.

2. The sodium phosphate buffer consisted of a 1:1 mixture of 0.67M NaH_2PO_4 and 0.67M Na_2HPO_4 (pH = 6.5 at 22 °C). For substrates not prone to chlorination, lower pH (3-4) can be employed to speed up the reaction.

3. *Caution*: It is not advisable to mix sodium chlorite solution and bleach prior to the addition since the mixture appears to be unstable. On a small scale, it is acceptable to mix the substrate, sodium chlorite, TEMPO, acetonitrile, and buffer first and then add bleach in one portion. The submitters report that the appearance of a greenish off-gas appeared in some instances. The use of a nitrogen or carbon dioxide sweep to carry the off-gas to an aqueous Na_2SO_3 trap can be used in these cases.

4. The progress of the reaction is monitored by HPLC: YMC ODS-AM column, 4.6x250mm, flow rate 1.00mL/min, 30 °C, linear gradient 20-80% MeCN/15 min, 0.1% H_3PO_4; retention time **1f**: 9.09 min, **2f**: 9.25 min.

5. The pH of the aqueous layer should be 8.5 – 9.0.

6. The product exhibits the following properties: mp 86-88.5 °C (lit.[9] 86 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.59 (s, 2 H), 3.79 (s, 3 H), 6.88 (d, J = 8.5, 2 H), 7.19 (d, J = 8.5, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.4, 159.1, 130.7, 125.5, 114.3, 55.5, 40.4; HPLC purity >99 area %.

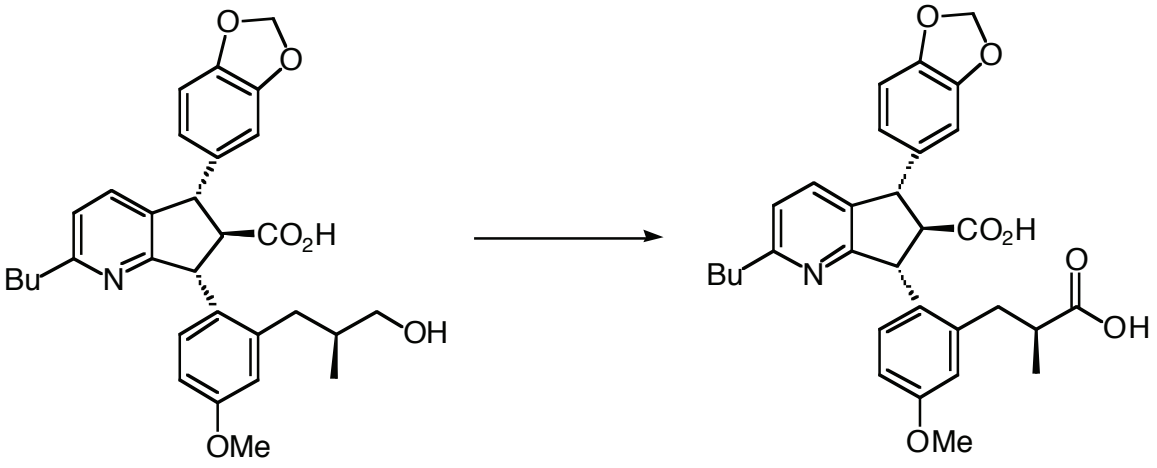
Waste Disposal Information

All toxic material were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academic Press; Washington, DC, 1996.

3. Discussion

The procedure described here provides an efficient and environmentally benign method for oxidizing primary alcohols to carboxylic acids using stoichiometric $NaClO_2$, catalytic TEMPO, and NaOCl. Compared with the previously reported TEMPO/NaOCl/CH_2Cl_2 protocol,[5c] this new procedure gives significantly improved yields and purity of the desired product by reducing the chlorination of the aromatic groups. No racemization or epimerization is observed for substrates with labile chiral centers. Additionally, no chlorinated solvent is required. Similar to TEMPO/NaOCl, this procedure is not applicable to alkenic alcohols and substrates with exceedingly electron-rich aromatic groups.

The development of this procedure stems from our recent work involving the oxidation of primary alcohol **1** to the carboxylic acid **2**.[3]



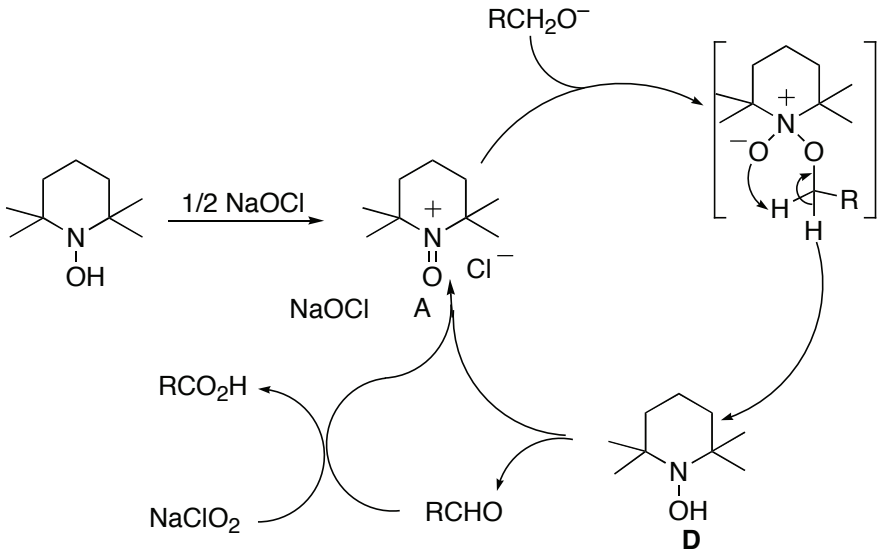
1 **2**

The submitters found that the $RuCl_3/H_5IO_6$ protocol[4] gave low yields (<50%) due to the destruction of the electron-rich aromatic rings. TEMPO catalyzed oxidation[5] with NaOCl also gave unsatisfactory results because of

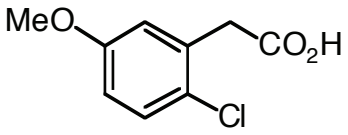
the chlorination of the aromatic groups. Other oxidants, such as H_2O_2, $MeCO_3H$, t-BuO_2H, etc., were examined without much success. In the submitters' recent report[7] on a CrO_3 (1 mol%) catalyzed oxidation, although it is much improved over the Jones oxidation in terms of environmental impact, the heavy metal issue is not completely eliminated. Investigation of the TEMPO/NaOCl protocol using sodium chlorite ($NaClO_2$)[8] as the oxidant resulted in the development of this new procedure.[3b] The reaction appeared to be very slow (~2%/h) initially. Subsequently, it was found that NaOCl dramatically accelerated the reaction. The conversion reached >50% in 1 h and went to completion in 2-4 h.

The remarkable acceleration can be explained by the proposed catalytic cycle shown in Scheme 1. TEMPO radical is first oxidized by NaOCl to the *N*-oxoammonium ion[5] **A**, which rapidly oxidizes the primary alcohol (**1**) to the aldehyde (**3**) and gives a molecule of the hydroxylamine **D**.[5] The aldehyde (**3**) is then oxidized by $NaClO_2$ to the carboxylic acid (**2**)[6] and regenerates a molecule of NaOCl. The hydroxylamine **D** can either be directly oxidized to **A** or undergo a syn proportionation with a molecule of **A** to give two molecules of TEMPO radical which can be oxidized back to **A**[5a,b] Although the exact mechanism of TEMPO-catalyzed oxidation of alcohols is still unclear, previous work[5] has shown that *N*-oxoammonium ion **A** and hydroxylamine **D** are involved. It is also known that $NaClO_2$ can readily oxidize aldehydes to the carboxylic acids in the absence of TEMPO.[6] The long induction period of the reaction without a catalytic amount of bleach is likely due to the relatively slow oxidation of TEMPO radical or the hydroxylamine **D** by $NaClO_2$. Once the reaction is initiated, it becomes self-sustaining as NaOCl is continuously regenerated. The chlorination problem is greatly reduced because the concentration of NaOCl remained low throughout the reaction. Risks for epimerization of the neighboring chiral center are also reduced since the labile aldehyde intermediate is rapidly oxidized to the carboxylic acid by sodium chlorite.

Scheme 1. Catalytic Cycle for the TEMPO/NaOCl Catalyzed Oxidation



This method is mild and efficient and has been demonstrated on a variety of primary alcohols (Table 1). For comparison purposes, substrates with electron-rich aromatic rings were also subjected to the TEMPO/NaOCl oxidation[5c] (entries 3, 5-7, 10). In all of these cases, much improved yields were obtained with this new procedure. The most striking example is **1g**. The yield of the desired product **2g** was only 42% using stoichiometric NaOCl in contrast to the quantitative yield obtained using our procedure (entry 7). One of the major side products in the oxidation with stoichiometric NaOCl was isolated and identified as the chlorinated compound **4** (Figure 1) based on NMR studies (NOE). Similarly, 3-phenylpropargyl alcohol (**1h**) was oxidized to the acid **2h** in 90% yield using our procedure vs. < 5% with NaOCl. It appeared that carbon-carbon triple bonds can be tolerated, but substrates with ordinary carbon-carbon double bonds such as cinnamyl alcohol failed to react. This was likely due to quenching of the catalytic NaOCl, which shut down the catalytic cycle. Substrates with very electron-rich aromatic groups such as **1n**-**1o** (Figure 1) also failed for similar reasons. Surprisingly, oxidation of 4-methoxybenzyl alcohol (**1p**) was very sluggish. Substrate **1i,** which contained a cyclopropyl group, posed no problem (entry 9). Chiral alcohols, including protected amino alcohol **1l**, were oxidized to the corresponding carboxylic acids without racemization (or epimerization) of the labile chiral centers (entries 10-12).



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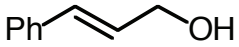
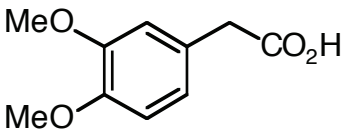
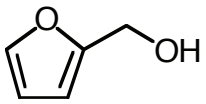


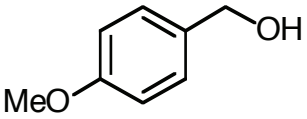
1m



1n



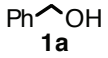
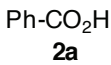
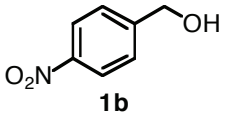
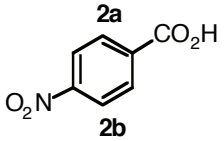
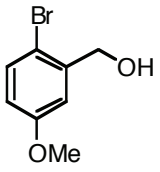
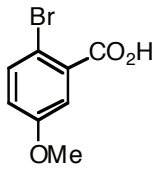
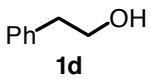
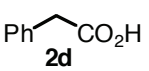
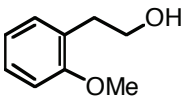
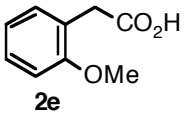
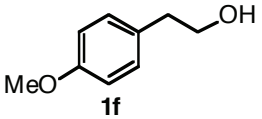
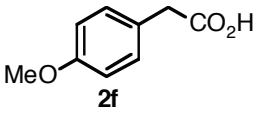
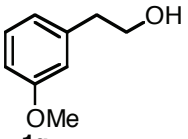
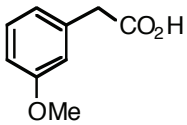
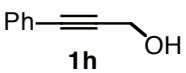
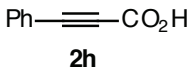
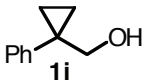
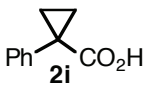
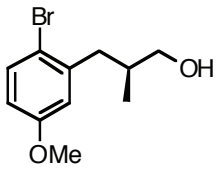
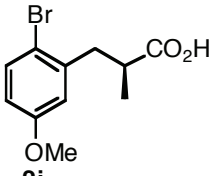
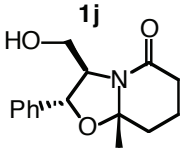
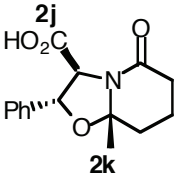
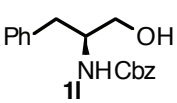
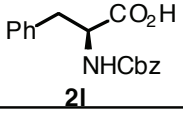
1o



1p

Figure 1

Table 1. **TEMPO** Catalyzed Oxidation of Primary Alcohols

Entry	Substrate	Product	Yield % ($NaClO_2$)	Yield % (NaOCl)
1	 **1a**	 **2a**	98	–
2	 **1b**	 **2b**	100	–
3	 **1c**	 **2c**	96	80
4	 **1d**	 **2d**	100	–
5	 **1e**	 **2e**	99	65
6	 **1f**	 **2f**	100	86
7	 **1g**	 **2g**	96	42
8	 **1h**	 **2h**	90	< 5
9	 **1i**	 **2i**	95	–
10	 **1j**	 **2j**	92	60
11	 **1k**	 **2k**	95	–
12	 **1l**	 **2l**	85	–

[a] All entries except **3, 9** and **10** were checked. The reactions took 6-10 h for completion in all cases. Additional charges of both $NaOCl_2$ and NaOCl, however, showed faster rate. Entry **11** was particularly sluggish towards oxidation. Yields and purities of products were generally comparable to those reported in the Table. For substrates not prone to chlorination, lower pH (3-4) can be employed to speed up the reaction.

1. Process Research, Merck Research Laboratories, Merck & Co. Inc., P.O. Box 2000, Rahway, NJ 07065

2. Pharm. R & D, Banyu Pharmaceutical Co. Ltd. Menuma, Saitama, Japan

3. (a) Song, Z. J.; Zhao, M.; Desmond, R.; Devine, P.; Tschaen, D. M.; Tillyer, R.; Frey, L.; Heid, R.; Xu, F.; Foster, B.; Li, J.; Reamer, R.; Volante, R.; Grabowski, E. J. J.; Dolling, U. H.; Reider, P. J.; Okada, S.; Kato, Y.; Mano, E. *J. Org. Chem.* **1999**, *64*, 9658-9667. (b) Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1999**, *64*, 2564-2566.

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9. CRC Handbook of Data on Organic Compounds, **1985**, HODOC No:04247.

Appendix
Chemical Abstracts Nomenclature (Registry Number)

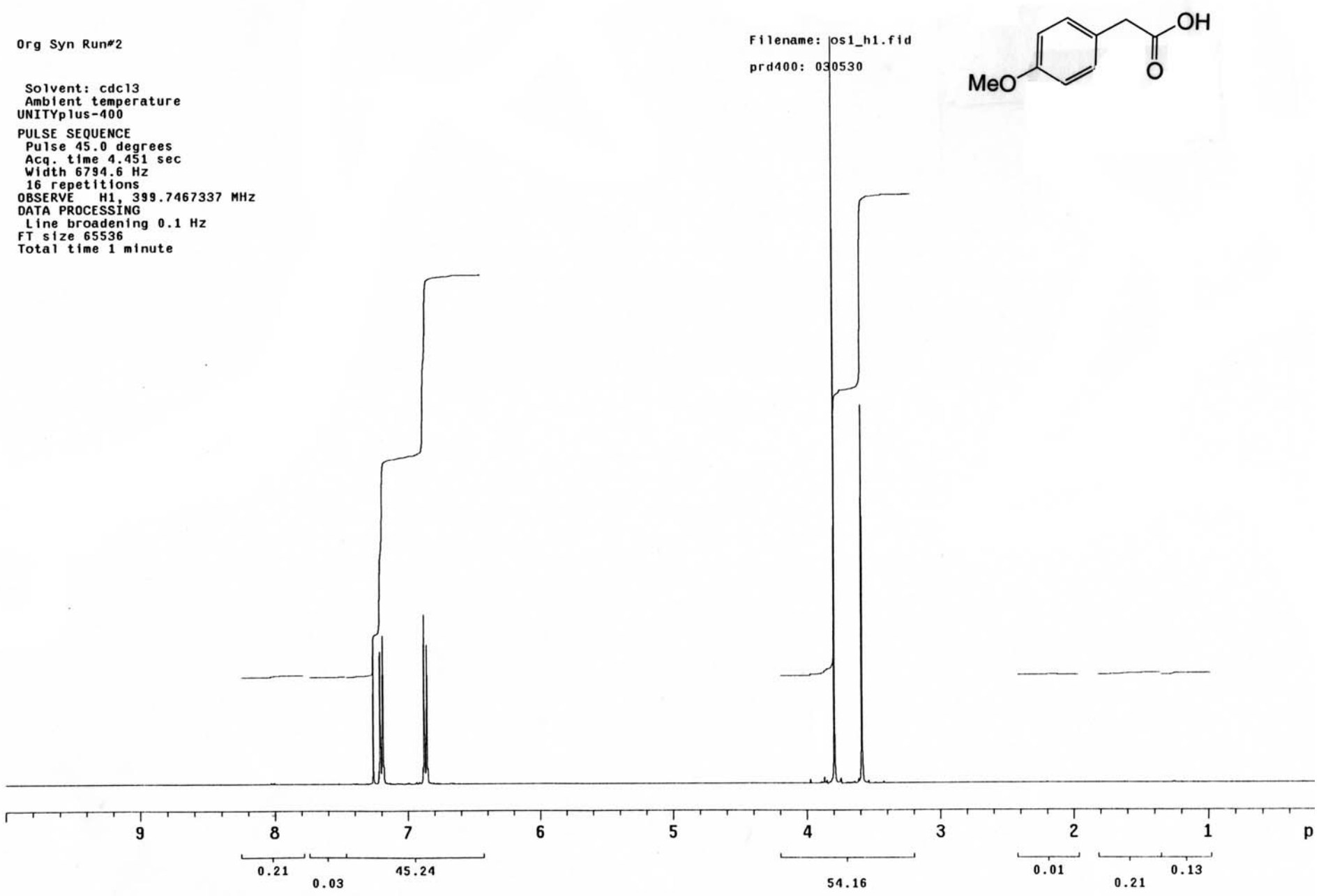
4-Methoxyphenethyl alcohol: Benzeneethanol, 4-methoxy-; (702-23-8).4-Methoxyphenylacetic acid: Benzeneacetic acid, 4-methoxy-; (104-01-8).

2,2,6,6-Tetramethyl-1-piperidinyloxy (TEMPO): 1-Piperidinyoxy, 2,2,6,6-tetramethyl-; (2564-83-2).

Sodium chlorite: Chlorous acid, sodium salt; (7758-19-2).

Sodium hypochlorite: Hypochlorous acid, sodium salt; (7681-52-9).

Methyl tert-butyl ether; Propane, 2-methoxy-2-methyl-; (1634-04-4).


Org Syn Run#2
Solvent: cdcl3
Ambient temperature
UNITYplus-400
PULSE SEQUENCE
Pulse 45.0 degrees
Acq. time 4.451 sec
Width 6794.6 Hz
16 repetitions
OBSERVE H1, 399.7467337 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 1 minute
Filename: os1_h1.fid
prd400: 030530
MeO
OH
O
9
8
7
6
5
4
3
2
1
p
0.21
0.03
45.24
54.16
0.01
0.21
0.13