

Synthesis of an Amine–Oleate Derivative Using an Ionic Liquid Catalyst

ATANU BISWAS,^{*,†} BRAJENDRA K. SHARMA,^{‡,§} KENNETH M. DOLL,[‡] SEVIM Z. ERHAN,[#]
JULIOUS L. WILLETT,[†] AND H. N. CHENG^{⊥,⊗}

[†]Plant Polymer Research and [‡]Food and Industrial Oil Units, National Center for Agricultural Utilization Research, Agricultural Research Service, U.S. Department of Agriculture, 1815 North University Stret, Peoria, Illinois 61604, [§]Department of Chemical Engineering, Pennsylvania State University, University Park, Pennsylvania 16802, [#]Eastern Regional Research Center, Agricultural Research Service, U.S. Department of Agriculture, Mermaid Lane, Wyndmoor, Pennsylvania 19038, and [⊥]Ashland Hercules Water Technologies, 500 Hercules Road, Wilmington, Delaware 19808. [⊗]Present address: Southern Regional Research Center, Agricultural Research Service, U.S. Department of Agriculture, 1100 Robert E. Lee Boulevard, New Orleans, Louisiana 70124.

A facile (and environmentally friendly) reaction between epoxidized methyl oleate and aniline to produce an oleate–aniline adduct, without the formation of fatty amide, was discovered. This reaction was carried out neat, with a catalytic amount of an ionic liquid. No solvent was used, no byproducts were produced, and the ionic liquid could be recovered and recycled. The reaction products were fully characterized by NMR and GC-MS.

KEYWORDS: Epoxidized methyl oleate; aniline; branched oleochemical; lubrication fluid

INTRODUCTION

Oleic acid is the major component of triacylglycerol in olive oil, and it is also a significant part of other vegetable oils. It is considered to be a healthy material, and many “high-oleic” oils are known (1). It is also known to have medicinal uses; for example, it has a hypotensive effect (2a) and may hinder the progression of adrenoleukodystrophy (ALD), a fatal disease that affects the brain and adrenal glands (2b, 2c). Its potassium salt and other derivatives are known as low-risk pesticides for agriculture (3). As an industrial product, oleic acid and its methyl ester are important oleochemicals used for the development of novel substances. In addition to food, oleic acid and its derivatives are used in many commercial applications, for example, detergents and soaps (4–6), lubricants (7–11), cosmetics (12–15), and emulsifying agents (16–18).

For some time we (11, 19–22), and others (7, 23–26), have been exploring new reaction pathways using natural materials. Because of its use in food, medicine, and agriculture, we are interested in oleic acid and its possible derivatives. We have developed a straightforward and environmentally friendly reaction to functionalize methyl oleate with a model aryl amine moiety (Scheme 1). This reaction was carried out neat, with a catalytic amount of an ionic liquid and without solvents or formation of byproducts. In previous work with fatty acid esters and amines, a common side reaction is the formation of fatty amides (24). In this new reaction, amides are not formed.

Time studies and mechanistic implications were investigated in this work. It may be useful to note that this reaction proceeds most easily for aryl amines. The resulting product may have interesting

properties because of the aromatic and the amine functionalities. Through this reaction, it is also easy to incorporate additional functional groups on the aromatic ring to produce a family of structures related to methyl oleate. Caution is advised in the choice of the aryl amine. Whereas some aryl amines are used as drugs (e.g., sulfamethoxazole and procainamide) and as sunscreens (e.g., *p*-aminobenzoic acid and its esters), some arylamines (including aniline) are considered to be hazardous or toxic.

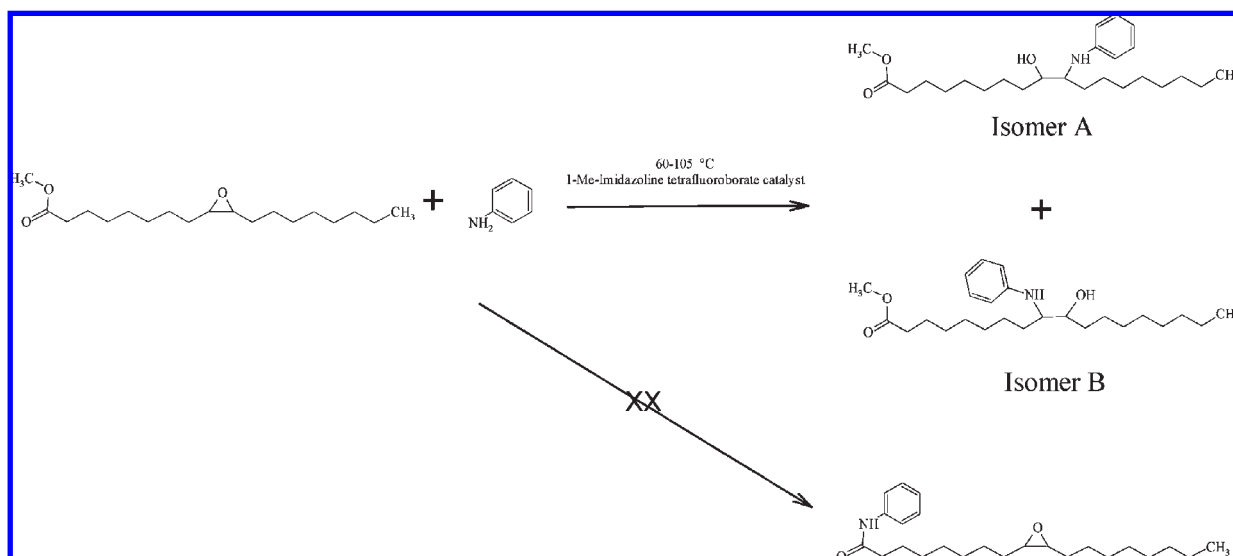
EXPERIMENTAL PROCEDURES

Materials. Methyl oleate (Tech 70%), hydrogen peroxide (ACS reagent, 30% Solution), formic acid (96%, ACS reagent), hexanes (>95%, HPLC grade), and aniline (99.5% reagent grade) from Sigma-Aldrich, St. Louis, MO; methyl oleate (>99%) from Nu-Chek Prep, Elysian, MN; 1-methylimidazole (99%) from Acros; tetrafluoroboric acid (48% min w/w aqueous solution) from Alfa Aesar; and NaCl (ACS reagent) and NaHCO₃ (ACS reagent) from Fisher, Fair Lawn, NJ, were all used as received.

Epoxidized methyl oleate (methyl 9,10-epoxy stearate; EMO) has been previously used in our laboratory to make a variety of different oleochemicals (21, 27, 28). The same synthesis was used here, which was adapted from that of Wool et al. (29) and originally based on Swern epoxidation (30, 31).

Instrumentation. GC-MS was performed on an Agilent (Santa Clara, CA) 7890A gas chromatograph equipped with a 7683B series injector and a 5975 C mass detector. The instrument programs and data acquisition were handled by a Windows XP equipped HP-Compaq DC7700 computer with a 3.39 GHz Pentium D processor using Agilent MSD Enhanced Chemstation version E01.00.237. The GC column was 30 m × 0.25 mm in dimensions with a film thickness 0.25 μm HP-5MS (Agilent). A helium flow rate of ~0.3 mL min⁻¹, an injection volume of 0.1 μL, and a 50:1 split ratio were used. The temperatures were as follows: inlet, 220 °C; detector, 220 °C; auxiliary transfer line, 250 °C; MSD, 150 °C. The initial temperature of

*Corresponding author (e-mail Atanu.biswas@ars.usda.gov).

Scheme 1. Reaction of EMO with Aniline Catalyzed by 1-Methylimidazole Catalyst^a

^aTwo isomers of the ring-opened product were observed, whereas a potential byproduct, a fatty amide, was not found.

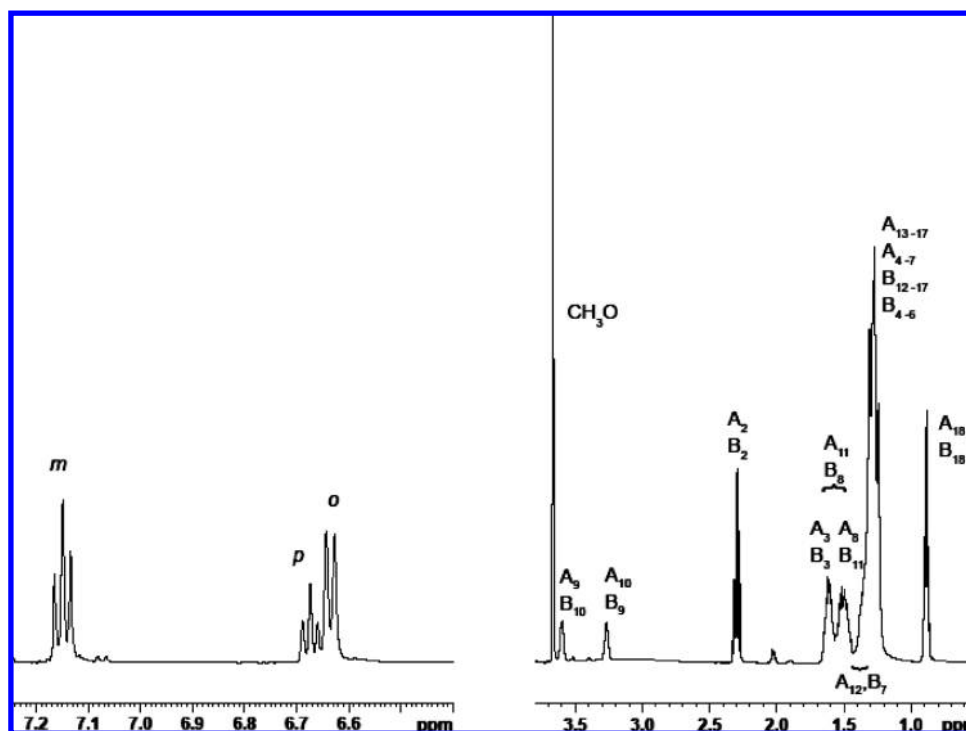


Figure 1. ¹H NMR spectrum of methyl oleate–aniline product.

150 °C was held for 2 min and then ramped to 280 °C at 15 °C min⁻¹, at which it was held for 20 min. The detector was run in the EI mode and set to scan for *m/z* ratios from 50 to 500 Da.

NMR was performed on a Bruker (Boston, MA) Avance 500 NMR spectrometer operating at 500 MHz for ¹H and 125 MHz for ¹³C. Bruker Icon NMR software was used on a HP x1100 Pentium 4 workstation. Peaks were referenced to sodium 3-trimethylsilylpropionate-2,2,3,3-*d*₄ (TSP) at 0.0000 ppm. Simulations of ¹³C NMR spectra were performed by ACD/Laboratories 6.00 ACD/CNMR predictor software, running on a Gateway Pentium 4 CPU with a 2.53 GHz processor.

Reactions. 1-Methylimidazolium tetrafluoroborate (32) was prepared by taking 1-methylimidazole (61.5 g, 0.75 mol) in a three-neck flask with a stirrer and cooled to 0 °C. Then tetrafluoroboric acid (0.75 mol, 40% solution in water) was added slowly over a period of 30 min with stirring and cooling to maintain the temperature at 0–5 °C. The reaction mixture

was stirred for an additional period of 2 h. Water was removed under vacuum to give the product as a colorless liquid, which solidified on cooling.

Aniline, 0.93 g (10 mmol) was added to an 8 dram (30 mL) glass vial containing 1.56 g (5 mmol) of epoxy methyl oleate and 0.0125 g of the ionic liquid, 1-methylimidazolium tetrafluoroborate (32). The mixture was stirred with a U-shaped stirring bar at room temperature for 5 min. It was allowed to stand for another 5 min so that the layers were separated before taking the zero time aliquot from the top layer. The mixture was covered with a septum and placed in a Reacti-therm reactor set at 105 °C. Samples were withdrawn after 1, 2, 4, 6, 8, 24, and 48 h.

After the final sample had been withdrawn, the remaining mixture was transferred to a 125 mL separatory funnel with 30 mL of ethyl acetate, which was washed three times with 50 mL of water. The water layer was discarded, the water wash was repeated twice, and a wash with a saturated

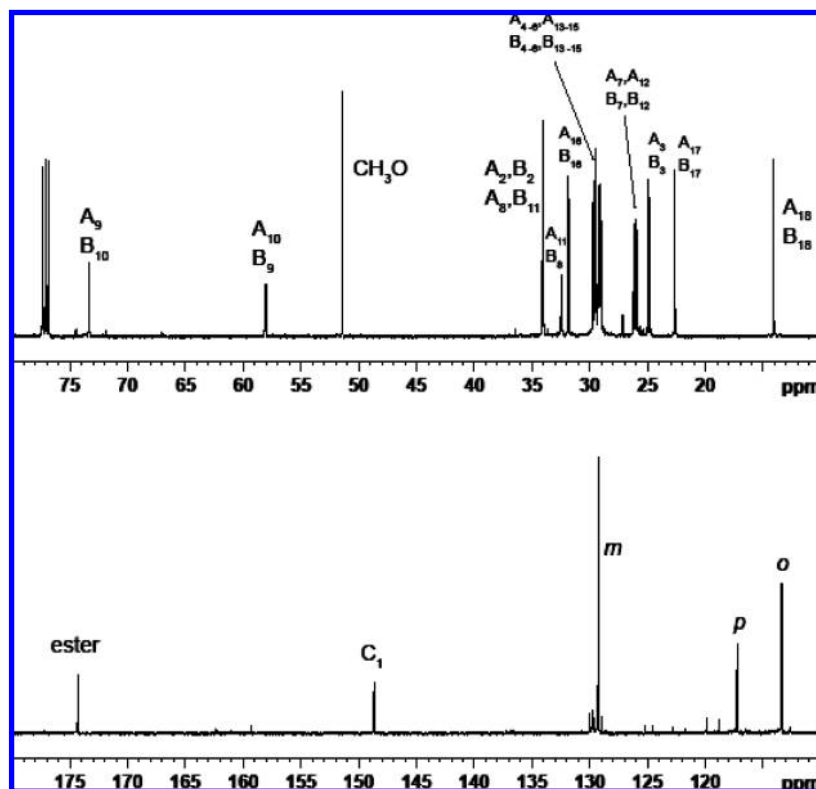


Figure 2. ^{13}C NMR spectrum of methyl oleate–aniline product.

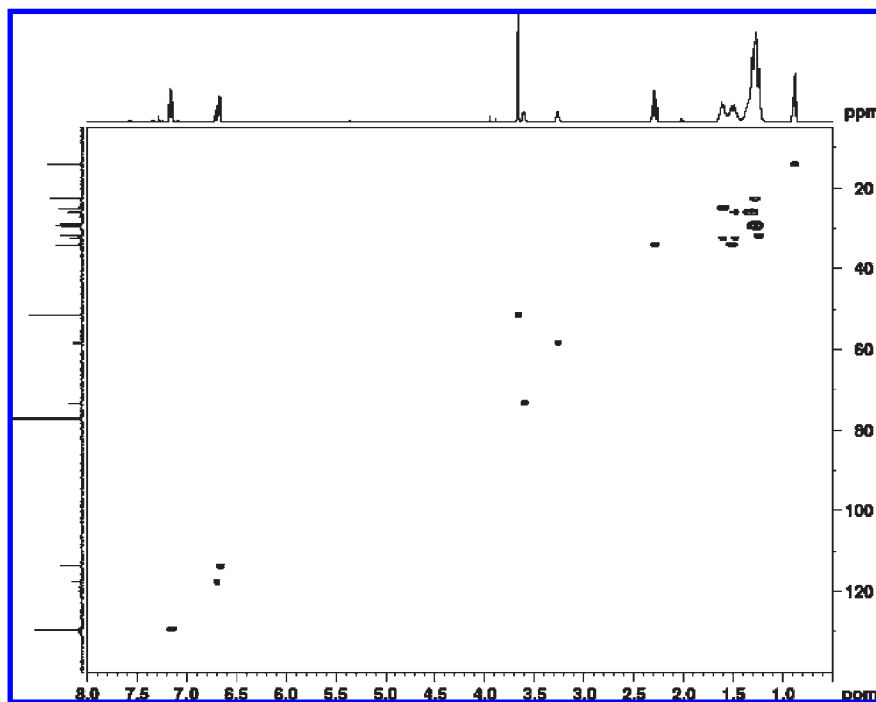


Figure 3. ^{13}C – ^1H HSQC plot for methyl oleate–aniline product.

solution of sodium chloride was performed. The ethyl acetate layer was transferred to a 100 mL beaker; excess sodium sulfate was added and then filtered. The filtrate was collected in a round-bottom flask, from which ethyl acetate was evaporated under vacuum using a rotary evaporator. The flask was placed in a vacuum oven at 50 °C overnight. When larger amounts of ionic liquid were used, the water washes were collected and combined in a round-bottom flask. Water was evaporated under vacuum using a rotary evaporator. The ionic liquid recovered in the flask was kept in a vacuum oven at 50 °C overnight to evaporate the residual water.

RESULTS AND DISCUSSION

In the reaction sequence, we first start with methyl oleate and epoxidize it to form the epoxidized methyl oleate (EMO). Epoxidation is a standard procedure and can be done readily via hydrogen peroxide and formic acid catalyst. The EMO is then reacted with aniline in the presence of an ionic liquid, 1-methylimidazolium tetrafluoroborate (**Scheme 1**). We discovered that although the ionic liquid is essential for the reaction, only a

Table 1. Assignments of ^1H and ^{13}C Spectra of Methyl Oleate–Aniline Adduct

	chemical shift of carbon or proton no.																		OMe
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	
methyl oleate (O)																			
^1H		2.30	1.62	1.30	1.30	1.30	1.30	2.00		5.34	5.34	2.00	1.30	1.30	1.30	1.30	1.30	0.88	3.66
^{13}C	174.1	34.0	24.9	29.0	29.0	29.0	29.6	27.1	129.7	129.9	27.1	29.6	29.3	29.5	29.3	31.9	22.6	14.0	51.2
O-epoxide–aniline adduct (A)																			
^1H		2.31	1.62	1.29	1.29	1.29	1.30	1.50	3.60	3.27	1.50	1.38?	1.29	1.29	1.29	1.29	1.29	0.89	3.67
								1.53?			1.62	1.46							
^{13}C	174.3	34.06 ^a	24.89	29.5	29.5	29.5	25.98 ^b	34.11 ^d	73.42	58.23	32.50 ^c	26.18 ^b	29.5	29.5	29.5	31.86	22.65	14.1	51.3
O-epoxide–aniline adduct (B)																			
^1H		2.31	1.62	1.29	1.29	1.29	1.38?	1.50	3.27	3.60	1.50	1.30	1.29	1.29	1.29	1.29	1.29	0.89	3.67
							1.46	1.62			1.53?								
^{13}C	174.3	34.03 ^a	24.84	29.5	29.5	29.5	26.08 ^b	32.47 ^c	58.23	73.39	34.05 ^d	25.87 ^b	29.5	29.5	29.5	31.81	22.63	14.1	51.3

^a Assignments may be reversed. ^b Assignments may be reversed. ^c Assignments may be reversed. ^d Assignments may be reversed.

catalytic amount is needed, even loadings as low as 0.5% by weight of the reaction mixture (0.0125 g in 2.5 g of reaction mixture) is enough to form product.

The reaction is straightforward. The reactants are added together, without solvents, and heated to 60–100 °C for several hours. A time study has been conducted under various reaction conditions and progress monitored by taking reaction aliquots, which are analyzed by GC-MS. (It is important to do the washing procedure to samples, as any residual catalyst will cause damage to the GC column.) The product has been fully characterized by ^1H and ^{13}C NMR and GC-MS.

Structural Characterization. The ^1H and ^{13}C NMR spectra of the reaction products are given in **Figures 1** and **2**, respectively. The spectra are relatively complex with many peaks. This is because we have two regioisomers present, corresponding to the attack of aniline on either position 9 or position 10 of the epoxide (**Scheme 1**).

Despite the large number of distinctive carbons and proton present, we are able to achieve almost complete assignments through a combination of empirical shift rules (33), chemical shifts of analogous compounds (34–36), and two-dimensional NMR. For future reference, the ^1H – ^{13}C HSQC plot is given in **Figure 3**. The assignments are summarized in **Table 1**.

In the ^1H NMR, the assignment of the aniline moiety is straightforward from coupling patterns and intensities: ortho, para, and meta in decreasing shielding. Protons at the positions 9 and 10 can also be easily assigned because the methine attached to oxygen is more downfield than the methine attached to nitrogen. As for the other protons, we have the benefit of having the assignments of the methyl oleate-aza-dicarboxylate ester (34, 35). The use of the 2D HSQC data then completes the assignments. Note that protons at position 11 in product A (and position 8 in product B) show up as doublets due to asymmetry at position 10 in product A (and position 9 in product B) as a result of aniline addition.

In the ^{13}C NMR, the assignments reasonably follow the empirical shift rules (33). It is of interest that at 125 MHz, the two products A and B give distinctly different peaks for all carbons, except for C-18, and carbons from aniline, methoxy, and ester. Because the pairs of peaks are often very closely located, it is not always possible to positively differentiate the A and B products in each pair. Some reversal in assignments may be likely as indicated in the footnote of **Table 1**. It is of interest that product A is slightly more preponderant than product B. If this assumption is wrong, then some of the assignments need to be reversed.

Note also that in the ^{13}C spectra, there is only the ester peak at 174 ppm. No fatty amide peak is observed. The positions of

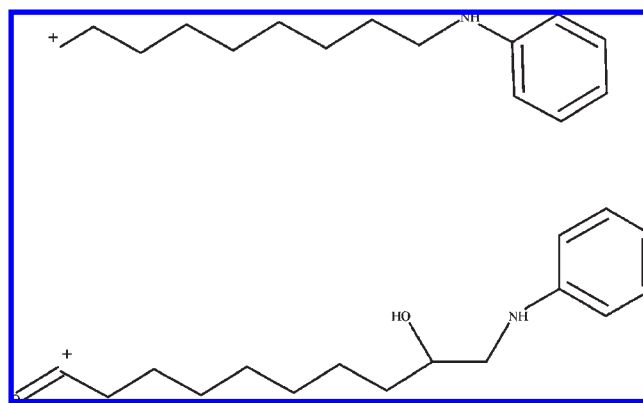


Figure 4. Two potential structures that correspond to the observed molecular weights in the EI MS of the products. The molecular formulas of $\text{C}_{15}\text{H}_{24}\text{N}$ and $\text{C}_{16}\text{H}_{24}\text{O}_2\text{N}$ have monoisotopic masses of 218.19 and 262.18, which correspond to the observed m/z peak in the spectra.

aniline ring carbons at 147.6 ppm (carbon attached to N), 113.5 ppm (ortho carbons), 117.2 ppm (para carbon), and 129.6 ppm (meta carbons) also confirm this observation. If the fatty amide had formed, these ring carbons would have appeared at 138.4 ppm (carbon attached to N), 121.6 ppm (ortho carbons), 124.4 ppm (para carbon), and 129.0 ppm (meta carbons). Similarly, the methoxy group is also intact (at 51.4 ppm), consistent with **Scheme 1**.

Additional evidence that the assigned product is correct has been shown by the MS detector on the GC. Although the molecular ion is not seen, as is expected for EI, the two largest peaks have m/z of 218.3 and 262.3 Da. These fragments can be assigned to the structures (**Figure 4**) of probable fragments of the proposed products, which have monoisotopic masses of 218.19 and 262.18 Da, respectively.

The study on the effects of different variables on the rate of production of products provided several interesting trends. These trends demonstrate the importance of temperature, catalyst concentration, and the molar ratio of EMO/aniline in this reaction.

Effect of Temperature. This novel reaction displays strong temperature dependence (**Figure 5**). The reactions were all conducted using 2.5 g of catalyst and a 1:2 EMO/aniline molar ratio. It is clear that the reaction rate increases at higher temperatures. At 2 h, the reaction run at 90 °C had nearly twice the amount of products (90%) as that performed at 60 °C (53%). Because the reaction conducted at 105 °C was complete in <2 h, reaction aliquots had to be taken more frequently to monitor the progress

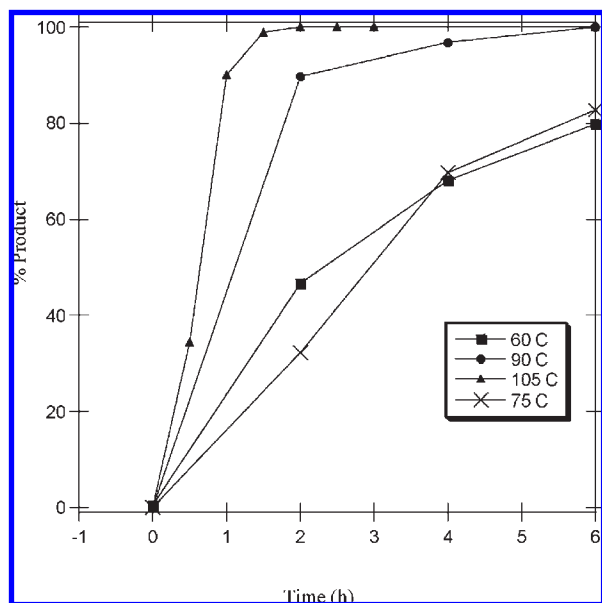


Figure 5. Observed production at various temperatures with a 2.5 g catalyst loading and a 1:2 EMO/aniline molar ratio. The reaction rate is considerably faster at 105 °C than at lower temperatures.

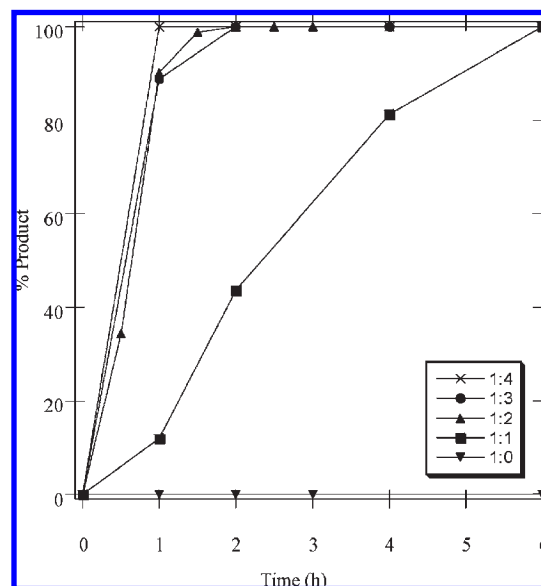


Figure 7. Observed production at varied EMO/aniline ratios at 105 °C with a 2.5 g catalyst loading. At a 1:1 molar ratio, the reaction is slower, but at ratios with excess aniline, the reaction is faster.

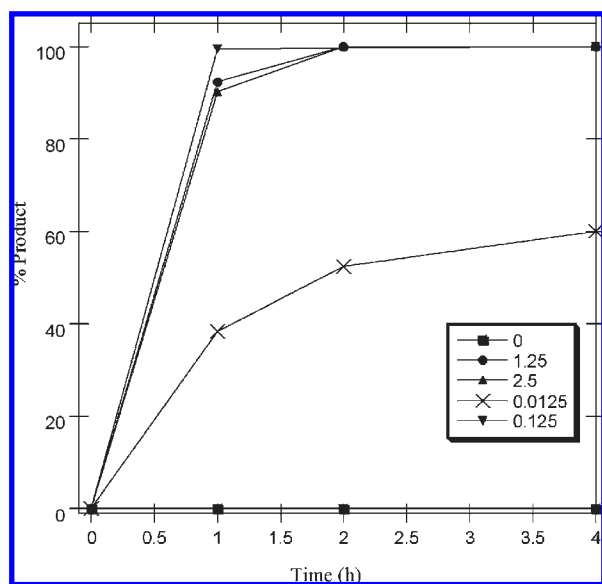


Figure 6. Observed production at various catalyst loadings at 105 °C with a 1:2 EMO/aniline molar ratio. The reaction proceeds quickly at catalyst loadings of 0.125 g (4.8% by weight of reaction mixture) or higher.

of the reaction. We have used this temperature in subsequent studies of catalyst and reactant ratio experiments.

Effect of Catalyst Concentration. We observed the effect of catalyst concentration by monitoring the initial 2–3 h of a series of reactions, conducted at 105 °C at a 1:2 EMO/aniline molar ratio, with different amounts of added catalyst (Figure 6). As expected, there is no product observed in the reaction without the catalyst. However, even 0.0125 g of catalyst (0.5% by weight of reaction mixture) is enough to cause considerable product formation. At an amount of catalyst of 0.125 g (5% by weight) or greater, the reaction nears completion in only 1 h.

Effect of EMO/Aniline Ratio. A final series of experiments, with differing molar ratios of EMO/aniline was performed at 105 °C with a 2.5 g catalyst loading (Figure 7). As expected, no

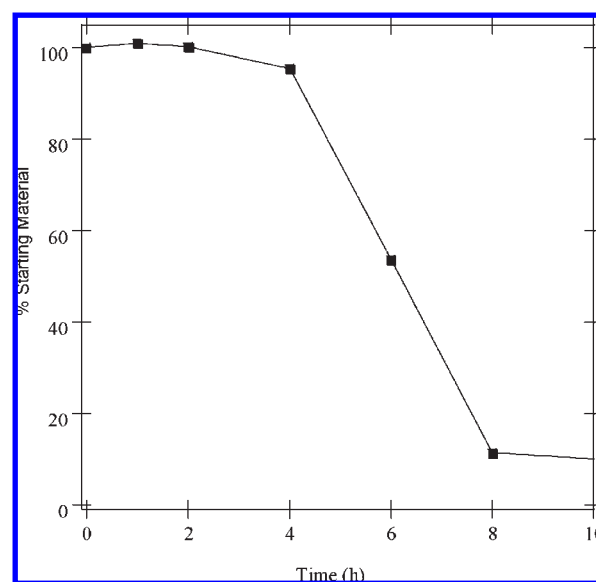


Figure 8. Observed loss of EMO in a reaction with no aniline present at 105 °C with 2.5 g of catalyst. The material is initially stable but, after an induction period, rapidly reacts.

product was formed without aniline. At 1 equiv of aniline, the products did form, but at a fairly slow rate. Nonetheless, the reaction achieved completion in 6 h. With 2 equiv of aniline, the reaction proceeded much more quickly, achieving near completion in an hour. Further excess of aniline had little additional effect.

In the experiment in which no aniline was used, we also monitored the loss of starting material, EMO. From this plot (Figure 8), it seems that initially the catalyst alone did not cause significant decomposition of the EMO, but after a long induction period, EMO loss became rapid. However, the product of this reaction was not observed by GC-MS, and the reaction was not studied further.

In summary, we report a straightforward and environmentally friendly reaction involving epoxidized methyl oleate and aniline.

The advantages of this reaction are that it is easily performed, gives good yield, and requires only a small amount of ionic liquid. Furthermore, the ionic liquid can be recovered and recycled. The reaction is a good method to introduce an aromatic amine onto the methyl oleate structure.

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