Ethyl L-Lactate as a Tunable Solvent for Greener Synthesis of Diaryl Aldimines
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The idea for this approach to making imines was conceived in July 2008. Preliminary data for 17 imines was published in *Green Chemistry* in February 2009. A provisional patent for this process was filed January 2010. The application for the conversion of the patent was published in August 2011 (Pub. No. US 2011/0196174). The method was used as part of a sophomore organic chemistry project during October 2010 when 76 different imines were synthesized and then again during October 2011 when nearly 100 different imines were synthesized.

Award Category: Academic

Focus Area 2: The use of greener reaction conditions

US Component: All work was completed within the United States at SUNY Oneonta.

Abstract:

Imines are essential intermediates in many reactions of pharmaceutical interest. For example, diaryl aldimines are used to synthesize blockbuster drugs such as Taxol® (used in chemotherapy) and Zetia® (used in cholesterol reduction). Diaryl aldimines are also used as additives to polyethylene to increase its rate of photodegradation in the environment. Unfortunately, traditional syntheses of diaryl aldimines are usually inefficient and environmentally unfriendly. They often use hazardous solvents and energy-intensive multihour reflux steps. Although some recent imine syntheses have successfully used more benign solvents or conditions, they still require long reaction times, recrystallization, or other procedures that negate some of the benefits of an otherwise greener synthesis.

Recently, Professor Bennett found that ethyl L-lactate, an FDA-approved food additive, can replace hazardous solvents commonly used to synthesize imines. Since then, she and her undergraduate research students have synthesized nearly 200 imines using this method and students in the teaching labs have made over 130 imines as part of a green chemistry project. The method is extremely efficient under ambient conditions and uses less solvent than published methods; it has a median yield of over 92% and a median reaction time of less than 10 minutes. The purity is such that recrystallization is unnecessary, avoiding additional waste. The key to the process is "tuning" the polarity of ethyl lactate by adding water to optimize reaction time, yield, and quality. The starting materials remain dissolved but the imine crystallizes out of solution as it is formed. Traditional methods often use water removal to drive the reaction forward. In contrast, Professor Bennett's method drives the reaction forward by removing the product through crystallization. A patent application for this method was published in 2011.

The imines synthesized by this method are now being studied for their effectiveness in biological and other applications. Several have already shown promise as fluorescent cell markers and antibacterial agents. All are fluorescent and some are photochromic. In summary, the ethyl lactate method is faster, usually results in higher purity and yield, uses less energy, uses less solvent, generates less waste, and uses a more benign solvent than published methods.

Chemistry of the technology

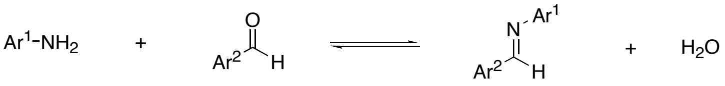

Figure 1. General synthesis of diaryl aldimines.

Diaryl aldimines are usually formed through a condensation reaction between primary anilines and benzaldehydes (Figure 1). Traditional syntheses usually require several hours of reflux and often include a water removal method, such as molecular sieves or a Dean-Stark trap. Common traditional methods include: toluene reflux with a Dean-Stark trap, dichloromethane with molecular sieves, or reflux in alcohol. Recently, our group discovered that ethyl lactate-water (ELW) solutions are effective alternatives to these more hazardous solvents for rapidly producing a large number of diaryl aldimines with excellent yield and purity under ambient conditions.[1] A patent application for this method was published in August 2011.

The method is simple. Briefly, 10 mmol of each starting material is dissolved separately in a portion of the solvent mixture, which is typically 5 mL ethyl lactate containing 0-30% water as cosolvent. The two components are combined, swirled until homogeneous, and then allowed to sit undisturbed at room temperature until there no longer appears to be any liquid present. The reaction mixture is then chilled on ice. Ice-cold brine, 10 mL, is added and the crystals are smashed with a spatula and mixed thoroughly. Crystals are recovered through vacuum filtration, rinsed with 10 mL ice-cold distilled water, and air dried. Recrystallization is rarely necessary.

We believe that the protic nature of the solvents (EL and water) helps to stabilize the transition state leading to the carbinolamine intermediate, promoting the necessary proton transfers and, in turn, accelerating the reaction. Another helpful characteristic is that the polarity difference between the reactants compared to the product imine is such that the reactants remain soluble but the product does not, causing the solvent to act as an effective crystallization medium. In contrast, many traditional solvents dissolve all of the reaction components, requiring the solvent to be removed later using energy-intensive methods such as rotary evaporation since the imines remain dissolved. Also noteworthy is water does not need to be avoided, contrary to conventional wisdom. According to Le Chatelier's principle, the equilibrium should be adversely affected by the presence of water (Figure 1) by shifting the equilibrium toward reactants. In contrast, the spontaneous removal of the product aldimine through rapid crystallization directly from the ELW solution outweighs any negative effect of water, thus elegantly illustrating how one equilibrium process can be harnessed to negate undesirable effects of another.

Professor Bennett's group initially published 17 diaryl aldimines using this method, all with high purity and yield, three of which are included in Table 1. No specialized equipment or conditions (Dean-Stark, inert atmosphere, or rotary evaporator), drying agents (molecular sieves, $MgSO_4$), magnetic or mechanical stirring, catalysts (Dowex resin, p-toluenesulfonic acid), or recrystallization was necessary. The only heat energy used was to help dissolve solid starting materials, though these would dissolve on their own given enough time. The few seconds used to facilitate dissolution was seen as a reasonable compromise. Various combinations of electron rich and deficient anilines and benzaldehydes were examined, all of which worked extremely well under these conditions. Thus, the method appears to be broadly applicable. As of December 2011, Professor Bennett's undergraduate research group has synthesized nearly 200 different imines and students in the organic teaching laboratories have synthesized more than half of these as part of a green chemistry project.

Many of the reactions are exciting to watch. In particular, the reaction between p-toluidine and salicylaldehyde (neither of which is fluorescent) forms a strongly fluorescent product. A video of this reaction under a 365 nm lamp is available on YouTube and can be accessed through ChemSpider (ID #10296919). The link is embedded at the end of the "Articles" section for this compound.

Problem addressed, its importance, and how this technology solves the problem

The problem that this technology addresses is that of how to synthesize imines in an environmentally friendly manner. This problem is important because of the current and potential uses of imines in a variety of industries, especially the pharmaceutical and materials industries. For example, some imines that have been synthesized by the ethyl lactate method are used to synthesize blockbuster drugs used for cancer treatment and cholesterol reduction. The methods currently used by the pharmaceutical companies, according to recent patents, are less environmentally friendly than this technology.

The most significant drawbacks associated with traditional imine syntheses are those related to the solvents used for the reaction and purification steps:

1. Air pollution: Traditional solvents are quite volatile and pose significant air pollution risk, especially since most are used under reflux conditions. In contrast, the volatility of ethyl lactate is comparatively much lower and, since it is used under ambient conditions, it has less chance of escaping into the atmosphere thereby decreasing the risk of air pollution.
2. Human toxicity: Traditional solvents (toluene, benzene, dichloromethane, ethanol, methanol) used for imine synthesis are known or suspected to be carcinogenic, mutagenic, and/or teratogenic according to their MSDS (Material Safety Data Sheet) information. In contrast, ethyl lactate is benign enough to be approved by the FDA as a food additive. Since it is used in lower volume under ambient conditions, it poses a minimal inhalation hazard.
3. Other pollution: Traditional methods require higher solvent volumes than the ethyl lactate method requires, usually 2-12 times higher. See Table 1 for volume comparisons on a 10 mmol scale. Since a higher volume is used, a greater amount of waste is generated (primarily liquid) and a greater potential for escape into the air is likely than possible with the ethyl lactate method. The ethyl lactate method results in decreased quantities of hazardous waste.
4. Flammability: Most traditional solvents are highly flammable (toluene, benzene, ethanol, methanol). While ethyl lactate is also quite flammable, it is generally used in much lower quantities and never heated during reactions, thus minimizing the potential for fires or explosions.
5. Feedstock type: Many traditional solvents originate from petrochemical (nonrenewable) resources (toluene, benzene). Ethyl lactate is a renewable feedstock.
6. Cost: Traditional methods are more expensive when all variables are considered (reactant and solvent cost, time, electricity usage, equipment needed, waste disposal, safety). See Table 1 for brief method comparisons.

How this technology compares with published methods

Table 1 shows a summary of how the ethyl lactate method compares with published methods. All ELW reactions were run under ambient conditions unless otherwise indicated. The reported melting points for the ELW syntheses are from *unrecrystallized* imines.

Table 1. Comparison of results from different methods. Literature methods in parentheses.

Imine Code (Citation)	Ar$_1$	Ar$_2$	Volume, Solvent, Temperature for 10 mmol scale	Time (min)	mp (°C)	Yield
pMeOpNO$_2$ (Schmeyers 1998)[2]	p-MeO- C_6H_4	p-NO$_2$- C_6H_4	26 mL 80% EL, (*solventless, 50°C, ODV*)	2 (*1440*)	133-134 (*134*)	96 (*100*)
pMeOpF (Bravo 1999)[3]	p-MeO- C_6H_4	p-F- C_6H_4	5 mL 100% EL (*17 mL benzene reflux, Dowex catalyst, DS, RE*)	3 (*180*)	95-97 (*97-98*)*	95 (*85*)
pMeOpH (Taxol®) (Sobanov 2006)[4]	p-MeO- C_6H_4	C_6H_5	5 mL 70% EL (*11 mL benzene reflux, DS, RE*)	2 (*180*)	68-70 (68)*	>99 (*77*)
pMeOCin[1] (Kronenthal 1982)[5]	p-MeO- C_6H_4	C_6H_5- CH=CH	5 mL 95% EL (*16 mL dichloromethane 0°, $MgSO_4$, N_2 atmosphere*)	1 (*150*)	116-119 (116-119)*	95 (*88*)
pMeOSal (Ibrahim 2006)[6]	p-MeO- C_6H_4	o-HO- C_6H_4	5 mL 90% EL (*6 mL EtOH 40-50°C*)	5 (*120*)	84 (*82*)*	98 (*82*)
pMeOpOH (Schmeyers 1998)[2]	p-MeO- C_6H_4	p-HO- C_6H_4	5 mL 80% EL (*solventless, ODV*)	2.5 (*480*)	210-211 (*210*)	>99 (*100*)
pEtOpF (Sandhar 2005)[7]	p-EtO- C_6H_4	p-F- C_6H_4	5 mL 80% EL (*10 mL EtOH, warm then ambient*)	0.3 (*overnight*)	97-99 (*90*)*	92 (*91*)
pPhOpMeO (Dikusar 2009)[8]	p-PhO- C_6H_4	p-MeO- C_6H_4	5 mL 100% EL (*60 mL MeOH reflux then 5°C*)	25 (*600-900*)	107-110 (*105-106*)	95 (*88*)
pMepF (Koschechko 2008)[9]	p-Me- C_6H_4	p-F- C_6H_4	5 mL 90% EL (*NR EtOH reflux*)	5 (*60-120*)	61-63 (*60-61*)*	95 (*80-90*)
pMepCl[1] (Schmeyers 1998)[2]	p-Me- C_6H_4	p-Cl- C_6H_4	5 mL 100% EL (*solventless, ODV*)	2 (*480*)	124-125 (*125*)	96 (*100*)
pMepOH (Schmeyers 1998)[2]	p-Me- C_6H_4	p-HO- C_6H_4	10 mL 90% EL (*solventless, ODV*)	2 (*120*)	218-219 (*215*)	98 (*100*)
pHpCl[1] (Hania 2009)[10]	C_6H_5	p-Cl- C_6H_4	5 mL 90% EL (*10 mL toluene reflux, MS, RE*)	6 (*120*)	63-64 (*60-62*)*	95 (*67*)
pBrpBr (Cianga 2006)[11]	p-Br- C_6H_4	p-Br- C_6H_4	5 mL 100% EL (*60 mL toluene reflux, acid catalyst, DS, N_2 atmosphere*)	2 (*360*)	140-141 (*141-142*)*	>99 (*82*)
pClpMeO (Bolognese 1991)[12]	p-Cl- C_6H_4	p-MeO- C_6H_4	5 mL 90% EL (*NR benzene reflux DS, RE*)	6 (*120*)	95-96 (*93-94*)*	97 (NR)
pClpOH (Schmeyers 1998)[2]	p-Cl- C_6H_4	p-HO- C_6H_4	5 mL 80% EL (*solventless, ODV*)	11 (*360*)	187 (187)	95 (*100*)
pFpBr (Minkin 1967)[13]	p-F- C_6H_4	p-Br- C_6H_4	5 mL 80% EL (*NR EtOH reflux*)	1 (*60-120*)	62-64 (*61*)*	96 (NR)
pFpMeO (Neuvonen 2007)[14]	p-F- C_6H_4	p-MeO- C_6H_4	5 mL 80% EL (*50 mL MeOH, RE*)	9 (*60*)	66 (*66-67*)*	91 (NR)
pFpBnO (Zetia®) (Magatti 1997)[15]	p-F- C_6H_4	p-BnO- C_6H_4	8 mL 100% EL (*25 mL iPrOH NR*)	8 (*overnight*)	130-131 (NR)*	98 (*92*)
pFpOH (Minkin 1967)[13]	p-F- C_6H_4	p-HO- C_6H_4	5 mL 70% EL (*NR EtOH reflux*)	3 (*60-120*)	182 (*180*)*	94 (NR)

*melting point of *recrystallized* compound; DS = Dean-Stark; MS = molecular sieves; RE = rotary evaporation; NR = not reported; ODV = oven dried under vacuum

Literature conditions or results that are better than the ELW method are indicated in *blue italics*; those that are worse are indicated in *red italics* to facilitate comparison.

The two imines included that are of current pharmaceutical interest are pMeOpH, which is used to synthesize Taxol®, and pFpBnO, which is used to synthesize Zetia®.[15]

Even the "greenest" of the published methods falls short when compared to the ELW method. For example, the first imine in Table 1 (and the first imine ever synthesized using the ELW system), pMeOpNO2, can be made using the solventless Schmeyers method. Often, solventless systems are perceived to be better than systems requiring solvent because so many reaction hazards are attributed to solvents. That said, once all parameters are considered, the ethyl lactate method is actually the greener method (See Table 2). The Schmeyers method uses no solvent but the reaction takes more than 700 times longer and requires at least 24 hrs more electricity consumption for heating the reaction and drying the product. There is no significant difference in the yield and melting point but the unrecrystallized imine from the ELW method is completely pure based upon proton NMR data.

Table 2. Detailed comparison of a solventless method with the ethyl lactate method.

pMeOpNO2	**Schmeyers**	**Ethyl lactate**
Solvent volume	0 (solid phase synthesis)	26 mL 80% ethyl lactate in water
Reaction time	24 hr	2 min
Reaction temperature	50°C	ambient
Work up	under vacuum at 80°C for unspecified amount of time	vacuum filtration with water aspirator; air dried overnight under ambient conditions
Other electricity used	none	<1 min to dissolve reactants
Yield	quantitative	96%
Melting point	134°C (unrecrystallized)	133-134°C (uncorrected and unrecrystallized)
Purity, by ^{1}H NMR	not reported	no contaminants evident in NMR

Realized or potential benefits and drawbacks throughout life cycle

- Realized benefit: lower toxicity of chemicals used
  - More benign solvent: Ethyl lactate is a renewable and biodegradable solvent that is FDA-approved as a food additive; has a relatively high boiling point (154°C) and thus poses a low inhalation hazard
  - No catalysts or other additives are necessary
- Realized benefit: decreased waste
  - Solvent: A lower volume of solvent used means less waste generated
  - Catalysts and additives: None are used thus no waste generated
  - Electricity: Very little electricity is used during and after the reaction so very little is wasted
  - Atom economy: The conditions are such that starting materials are completely consumed, rendering recrystallization unnecessary and thereby decreasing waste volume. *Note: several published methods have been performed for comparison. In all cases the unrecystallized imine from the ethyl lactate method was purer than recrystallized imine from the published methods according to proton NMR. In those cases where starting aniline and aldehyde were evident, the melting point was significantly higher than that in the published method, thus indicating that the level of impurities in the unrecrystallized imine from this method was lower than that in the published method where recrystallization was used.*

- Realized benefit: lower cost
    - Solvent: ethyl lactate is similar in cost to most other standard solvents but less volume is necessary, resulting in a lower cost
    - Other chemicals: no catalysts or other additives must be purchased
    - Electricity: far less electricity is used
    - Specialized equipment: no specialized equipment or glassware (such as a rotary evaporator or Dean-Stark trap) must be purchased.
- Realized benefit: broad applicability

  The method is applicable to a large variety imines. Nearly 200 aryl aldimines have been synthesized. In addition, several alkyl aryl aldimines and diaryl ketimines have been made (not reported here).
- Realized benefit: new compounds

  Out of the 150 compounds that have been searched in the literature, 8 have no record accessible through SciFinder Scholar.
- Realized educational benefits: effective and efficient enough to use in teaching labs as part of an unknown identification project and a subsequent reduction experiment

  In Fall 2011 semester students were given unique combinations of anilines and benzaldehydes to identify through spectroscopic techniques. They later reacted their unknowns together using the ELW method to form nearly 100 different imines with a median reaction time of less than five minutes and a median yield of 85%. During Spring 2012 these students will “recycle” their unique imine products to use in a “green” reduction experiment to synthesize secondary amines. This experiment was first conducted in Spring 2011 and resulted in 51 different amines. The imines are sufficiently stable for these purposes.
- Potential benefit: applicability to related syntheses

  We anticipate that the method will work well for similar reactions (e.g., hydrazones and semicarbazones). We also anticipate that the principles behind the method will work for reactions that currently require water removal methods to drive the reaction to completion. The principle behind solvent tuning has the potential to eliminate unnecessary waste by rendering purification steps unnecessary.
- Potential benefit: less expensive pharmaceuticals

  This method has the potential to save a great deal of money in the pharmaceutical industry through the decreased volume of solvent necessary, decreased number of chemicals required, decreased waste generated, decreased use of energy, and greatly decreased reaction time. In addition, less money in the form of wages would be required because the reactions are so fast and have much less active work time than traditional methods.
- Realized and potential benefits: new research directions.

  Several new projects have arisen from the ability to synthesize so many compounds so easily.
    - Use as biological fluorescent dyes: In collaboration with Dr. Nancy Bachman in the biology department, several imines have been tested in mouse fibroblast cells and analyzed by fluorescence microscopy. Some have shown specific binding to different cellular components (under investigation) and perform better than the dyes Dr. Bachman used to buy. Imines have replaced most of her expensive commercial dyes.
    - Antibacterial agents: the organic students have screened about 130 imines as part of their green synthesis project. Those that appeared to have activity against *E. coli* are now under investigation for activity against more pathogenic bacteria such as *S. aureus.* This project is also in collaboration with Dr. Bachman.

- Drawback: potential impurities in liquid waste stream

  The only known drawback to using this method is that it is unclear whether the impurities filtered from the crystals can ultimately enter the aqueous waste stream. Tiny quantities of the anilines, aldehydes, and imines *do* end up in the filtrate. That said, once filtrates are collected in a dedicated aqueous waste container and allowed to sit until the container is full, the impurities coagulate and can then be removed by filtration. After this filtration, there is no longer enough contamination from anilines, aldehydes, or imines to observe through ^{1}H NMR. All that is detectable in the waste solution at this point is water with some ethyl lactate. While there could still be impurities in the waste stream, those amounts are probably less than what occurs in traditional methods.

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