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Synthesis of Diphenylamine-Based Novel Fluorescent Styryl Colorants by Knoevenagel Condensation Using a Conventional Method, Biocatalyst, and Deep Eutectic Solvent

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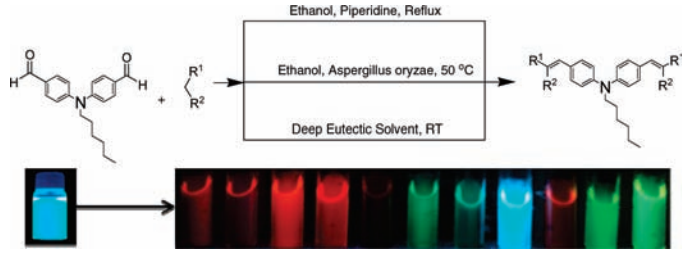
ABSTRACT



Novel Y-shaped acceptor−π-donor−π-acceptor-type compounds, synthesized from 4,4′-hexyliminobisbenzaldehyde as electron donors and different active methylene compounds as electron acceptors, were produced by conventional Knoevenagel condensation alone, with a deep eutectic solvent, or with a lipase biocatalyst to compare the yield and recyclability among the three methods. Yield, reaction time, reaction temperature, and recyclability were compared among the three methods. The photophysical properties and thermal stability of the products were also investigated.

Organic fluorescent heterocyclic chromophores have a wide range of applications in biochemistry, for example, in traditional textile coloration, molecular probes,[1] organic light-emitting diodes,[2] photovoltaic cells,[3] and mass coloration of polymers.[4] Electron acceptor isophorone derivatives, substituted phenyl acetonitrile compounds, and aliphatic active methylene compounds are used for the synthesis of chromophores. Traditional catalysts such as alkali metal hydroxides (e.g., NaOH and KOH), pyridine, and piperidine are used in condensation reactions. Basic zeolites, such as Cs-exchanged NaX (CsNaX) and GeX, Cs, Cs-lanthanum impregnated mesoporous MCM-41[5−7] and alkali-exchanged zeolites,[8] however, are also used.

The emerging area of green chemistry seeks to minimize environmental hazards as performance criteria in the design of new chemical entities. Biocatalysts in organic synthesis have attracted the attention of organic chemists because of their synthetic utility.[9−12] The high potential of lipases as biocata-

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lysts for organic synthesis are well recognized.[13] Lipases can be used in a wide variety of organic solvents without the need for coenzymes for their activity.[14] Lipases combine broad substrate recognition with high efficiency and selectivity. Therefore, lipases offer an excellent alternative to classical organic techniques in the selective transformation of complex molecules. Lipases are the most frequently used enzymes in organic synthesis because of their stability, ready availability, and their acceptance of a broad range of substrates.[15] The use of lipases is now well established in transesterification,[16] ester hydrolysis,[17] numerous applications in kinetic resolutions[18] or enantioselectivity syntheses based on meso compounds,[19] and amidation of racemic esters or amine,[20,21] but their application in Knoevenagel condensation has not been well explored. We focused our attention on the condensation of 4,4′-hexylimino-bisbenzaldehyde using lipase from *Aspergillus oryzae* with different active methylene compounds.

Ionic liquids have recently attracted increasing interest in the context of green synthesis. Ionic liquids were initially introduced as alternative green reaction media because of their unique chemical and physical properties of nonvolatility, nonflammability, thermal stability, and controlled miscibility.[22] Deep eutectic solvents (DESs), effectively eutectics formed between the two components, result in a very large depression of freezing point which can be in the region of 200 °C. The interaction between the ammonium salt and the hydrogen-bond donor is an example. Deep eutectic solvents have physical and solvent properties similar to those of ionic liquids formed with discrete ions. Abbott et al.[23] published a series of studies on the low melting point of deep eutectic liquid systems based on choline chloride ([Ch][Cl]). Choline is a naturally occurring biocompatible compound that is not hazardous if it is released back into nature as choline or its deep eutectic mixture.[24] Urea is a compound present in all animals. Because choline chloride and urea are both inexpensive, processes that use this deep eutectic solvent are also economically viable. Many ionic liquids leave hazardous materials in the environment. Their toxicity is similar to or higher than that of organic solvents.[25,26] An alternative approach to overcome these drawbacks is the development of a deep eutectic solvent from components that are nontoxic to the environment, possess biodegradable properties, or are obtained from biodegradable resources, and are readily available and inexpensive. The ability of a deep eutectic mixture to serve as a solvent has not been extensively explored in the field of synthetic organic chemistry. We now report a Knoevenagel reaction using a deep eutectic solvent.

A series of novel diphenylamine-based chromophores **a**−**k** was synthesized in which the acceptors were attached to the central diphenylamine group by a traditional Knoevenagel condensation using piperidine as the base in ethanol solvent at reflux temperature. Three different types of active methylene compounds, i.e., aliphatic, substituted phenyl acetonitrile, and isophorone-based active methylene compounds, were introduced at the peripheral phenyl groups. The results of the experiments are summarized in Table 1. Use of the conventional method required a higher temperature and longer reaction time; however, in some cases (**c** and **h**−**k**) reaction time using the conventional method was shorter as compared to the lipase-catalyzed reaction. The lowest yield observed in **b** and **c** in the lipase-catalyzed reaction may be attributed to the weaker nature of the active methylene compound due to the presence of amide linkage. In entry **i**, the yield is markedly less due to the weaker nature of active methylene compound.

A biocatalyst was used to explore its synthetic utility in Knoevenagel condensation. The reaction mechanism of the condensation using a biocatalyst involved a sequential dehydration process. The active site of lipase functions as a nucleophile, which condenses the acidic proton of the active methylene group, and then dehydration gives a carbon−carbon double bond. To optimize the reaction parameters, the reaction of 4,4′-hexyliminobisbenzaldehyde with ethyl cyano acetate in the presence of lipase was selected as a model reaction. Optimum results were obtained when reactions were conducted in the presence of 50 mg (10% by weight of aldehyde) of lipase for 4.72 mmol of aldehyde at 50−55 °C. No major change in the product yield was observed when 20% (by weight of aldehyde) lipase catalyst was used. No product formed when the reaction mixture was stirred at 60 °C for 15 h in the absence of lipase. Under the optimum conditions, aldehyde was condensed with different active methylene groups in the presence of lipase, giving moderate to good yield of the product. To make the biocatalytic processes more economical on a large scale, the recyclability of lipase must be considered. During this study, lipase was recycled for up to four cycles. There was no significant decrease in product yield after completion of the first cycle, but the yield declined up to 50% after the completion of the fourth cycle (Table 3).

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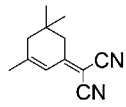
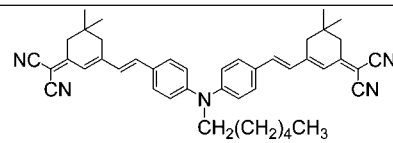
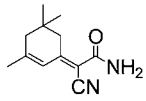
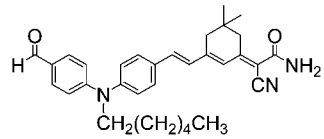
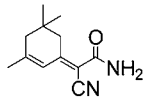
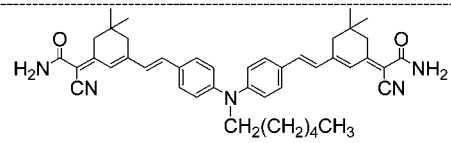
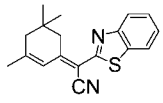
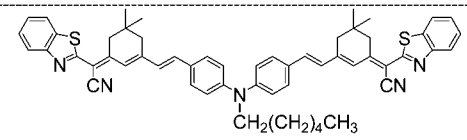
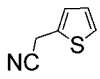
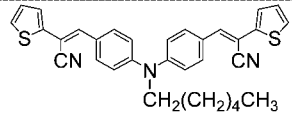
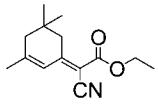
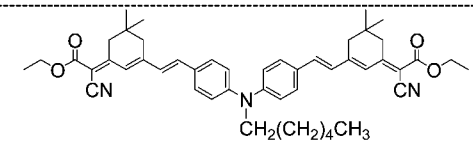
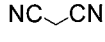
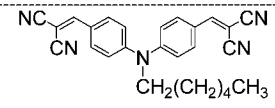
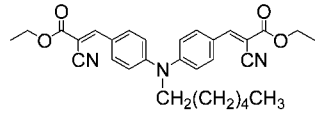
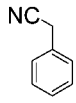
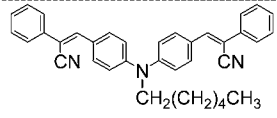
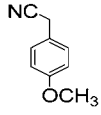
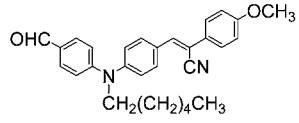
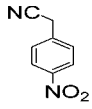
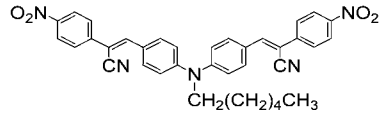
Table 1. Results of Knoevenagel Reaction in Three Different Conditions

Entry	Active methylene compounds	Products	Yield[a]%, temp. in °C, time (h)	Yield[b]%, temp. in °C, time (h)	Yield[c]%, temp. in °C, time (h)
a.			85, Reflux, (4)	78.5, 50-55, (2)	95.3, 25-30, (0.25)
b.	 1 mole		62, Reflux, (6)	60.5, 50-55, (2)	83.5, 25-30, (0.25)
c.	 2 mole		75, Reflux, (6)	50.5, 50-55, (15)	90.9, 25-30, (0.33)
d.			82, Reflux, (5)	82, 50-55, (5)	92.2, 25-30, (0.25)
e.			77, Reflux, (5)	66, 50-55, (4)	88.2, 25-30, (0.5)
f.			74, Reflux, (5)	78, 50-55, (4)	90.5, 25-30, (0.25)
g.			85, Reflux, (2)	95, 50-55, (1)	94.5, 25-30, (0.25)
h.			79, Reflux, (4)	90, 50-55, (8)	93.3, 25-30, (0.25)
i.			61, Reflux, (5)	65, 50-55, (9)	75.0, 25-30, (0.25)
j.			64, Reflux, (6)	85, 50-55, (15)	83.3, 25-30, (0.25)
k.			73, Reflux, (6)	90, 50-55, (8)	92.3, 25-30, (0.25)

[a] Yield by conventional Knoevenagel condensation. [b] Yield by lipase- catalyzed reaction. [c] Yield by deep eutectic solvent.

The problems of a longer reaction time, use of toxic bases, higher temperature, selectivity, difficulty in product separation, and recyclability of lipases were approached using green technology, i.e., a deep eutectic solvent. A deep eutectic solvent was easily prepared by a previously reported method[23] with 100% atom economy. Choline chloride (1 mol) was reacted with urea (2 mols) at 80 °C. The resulting molten salt was used directly in reactions without purifica-

tion. This method produced no byproducts; therefore, there was no loss during isolation of the solvent. Recycling of the deep eutectic solvent was also effectively achieved by the representative reaction of compound (**a**) and could be performed five times without a significant decrease in the product yield. There was no need for further purification of the deep eutectic solvent before its reuse for the same transformation. The reactions using the recycled deep eutectic solvent also showed good results.

The effect of reaction time on conversion was investigated. Increasing the temperature up to 60 °C and prolonging the reaction time did not significantly improve the reaction.

Key intermediate 4,4′-hexyliminobisbenzaldehyde was synthesized by *N*-hexylation of diphenylamine, followed by Vilsmeier−Haack formylation. Isophorone derivatives were synthesized from isophorone using different active methylene compounds. All colorants were soluble in common organic solvents, such as chloroform, dichloromethane, 1,2-dichloroethane, acetonitrile, tetrahydrofuran, and *N*,*N*-dimethylformamide due to the introduction of long hexyl chains in the compounds. The structures of these compounds were elucidated by FTIR, ^{1}H NMR, and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis. The coupling constant ($J \approx$ 16 Hz) of olefinic protons in purified chromophores indicates that the reaction afforded trans isomers.

Knoevenagel condensation of 4,4′-hexyliminobisbenzaldehyde with a variety of active methylene compounds viz. 2-(3,5,5-trimethylcyclohex-2-enylidene)malononitrile, (2*E*)-2-cyano-2-(3,5,5-trimethylcyclohex-2-enylidene)acetamide, (2*E*)-2-(benzo[d]thiazol-2-yl)-2-(3,5,5-trimethylcyclohex-2-enylidene)acetonitrile, (2*E*)-2-cyano-2-(3,5,5-trimethylcyclohex-2-enylidene)acetate, 2-(4-methoxy phenyl)acetonitrile, 2-phenylacetonitrile, 2-(4-nitrophenyl) acetonitrile, 2-(thiophene-2-yl)acetonitrile, ethyl 2-cyanoacetate, and malononitrile was performed.

Here we describe the synthesis and photophysical studies of novel synthesized diphenylamine-based styryl molecules that are potential candidates for application in organic electronics. The linear long alkyl chain was introduced to a 4,4′-hexyliminobisbenzaldehyde **4** moiety to improve the solubility of the resulting fluorescent compounds in common organic solvents.

Absorption and photoluminescence spectra of the dyes in dichloromethane (1×10^{-4} M) solution were consistent with our expectation. The absorption maxima were in the range of 385−525 nm. The absorption maxima, Stokes shifts, of the isophorone based dyes **a**−**d** and **f** varied in the range of 88−166 nm, which is a significantly greater variation than for other simple styryl dyes (Table 2, see the Supporting Information). As expected, the bathochromic shift of colorants **a**−**d** and **f** in the absorption band showed higher absorption maxima and a larger Stokes shift because of the isophorone-bridged conjugation system. These extended chromophores displayed dramatically enhanced absorption, fluorescence properties, and a greater Stokes shift. The more conjugated molecule **d** displayed larger absorption maxima, a greater Stokes shift, and a larger molar absorption coefficient due to its relatively more extended conjugation. For given donor−acceptor compounds, the Stokes shift increase was associated with the conjugation length increase. Compound **b**, however, showed a larger Stokes shift at 166 nm despite its shorter conjugation; perhaps because only one electron acceptor was condensed to an electron donor. The fluorescence spectra of dyes **a**−**k** in chloroform were recorded. Emission spectra were obtained using the excitation wavelength which is nothing but absorption maxima of respective compounds. The emission spectra of isophorone-based long conjugated compounds **a**−**d** and **f** were observed at 624, 586, 590, 658, and 588 nm, respectively (Table 2, see the Supporting Information). Absorption and emission maxima of **a**−**d** and **f** were significantly higher than those of chromophores **e** and **g**−**k**.

Compounds **a**−**k** were subjected to the thermogravimetric analysis to investigate their thermal stability. Stepwise isothermal ramping up to 600 at 10 °C/minute was performed in a nitrogen atmosphere. The change in the weight of the colorants was measured as a function of temperature. Thermal stability is defined as the temperature up to which ∼95% of the composition of the compound remains stable. For compound **a**, 94.75% of the weight composition was stable up to 314 °C and underwent rapid thermal decomposition thereafter. Colorants **e** and **g** were stable up to 362 and 325 °C, respectively. The compound containing a methoxy group (**j**) had the lowest thermal stability at 274 °C, possibly due to the labile nature of the methoxy group. These data indicate that all of these chromophores had good thermal stability and are therefore applicable for polymers requiring higher extrusion temperature ranges.

These dyes may become valuable colorants for high technologic applications. An efficient protocol has been developed for Knoevenagel condensation of aromatic aldehydes with an active methylene group as an ecofriendly reaction medium. The lipase catalyst exhibited activity and was reusable for up to four consecutive cycles. The reaction is applicable to a wide variety of active methylene compounds with aromatic aldehydes.

The Knoevenagel condensation using a readily available and biodegradable ammonium deep eutectic solvent (choline chloride/urea) also provides an efficient and convenient method without the use of other catalysts or organic solvents. This method offers marked improvements in terms of simplicity, decreased reaction time, simple reaction conditions, general applicability, high isolated product yields, and the use of environmentally benign procedures and solvents. This method also eliminates the use of hazardous organic solvents and toxic catalysts, and thus provides a better and practical alternative to existing procedures. It is easy to separate the catalyst and substrate after completion of the reaction. Deep eutectic solvents provide a good alternative for industrial synthesis as the reaction is readily scalable (Table 3, see the Supporting Information). We have synthesized a series of symmetrical and unsymmetrical chromophores with good thermal stability and photophysical properties by grafting donor at the core and strong acceptors at the edge of the periphery.

Supporting Information Available: Details of experimental procedure, structure characterization, and figures. This material is available free of charge via the Internet at http://pubs.acs.org.

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