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Sun Light Assisted Direct Amide Formation via a Charge-transfer Complex

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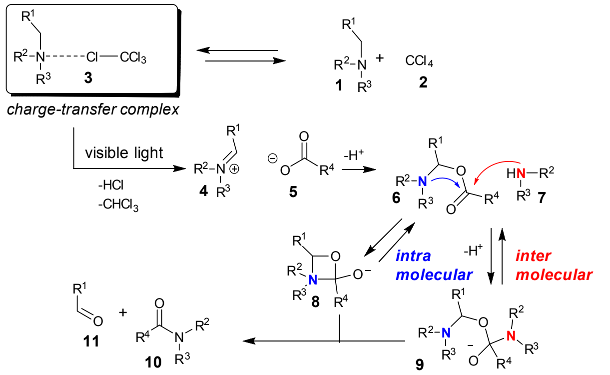
We report on the use of charge-transfer complexes between amines and carbon tetrachloride, as novel way to activate the amine for photochemical reactions. This principle is demonstrated in a mild, transition metal free, visible light assisted, dealkylative amide formation from feedstock carboxylic acids and amines. The low absorption coefficient of the complex allows deep light penetration and thus scale-up to gram scale.

Visible light-induced homogeneous photochemistry and photocatalysis has become a staple of research in organic synthesis in recent years.[1] Most reported modern applications use arc lamps or blue-light LEDs as the light source and transition metal complexes, mostly of ruthenium or iridium, as the light harvesting species and/or photocatalyst.[2] The development of flow systems has allowed for dramatic scale-up of these reactions to industrial scale. [3,1b,4] However, while the advantages of LEDs over conventional arc lamps, such as mercury lamps, is indisputable, an even more convenient and abundant light source is solar light. Indeed, the harvesting of solar energy for generating electricity[5] and fuels[6] are amongst the fastest growing research fields, involving both scientific and engineering aspects. While most LED-induced photochemistry has been developed in Europe and North America, a large segment of the developing world, including those undergoing rapid industrialization, has plentiful solar light available.[7] In addition, many synthetic photocatalytic processes rely on the use of heavy or rare metals such as a ruthenium and iridium which are expensive and could have detrimental environmental effects. Photochemistry and photocatalysis based on directly addressing inexpensive readily available organic reagents has received comparatively less attention.[8]

A drawback of many light-induced reactions is that the chromophores used are such potent absorbers of light that it does not penetrate deep enough into the solution, leading to problems with scalability. Indeed the aforementioned flow processes have been developed as an elegant solution to this issue but does require additional investment in infra-structure.[4]

In the present paper, we report a visible light assisted direct amide formation from feedstock carboxylic acids and amines. The importance and challenge of developing new amide bond forming reactions[9,10] is often overlooked due to the relative ease by which this reaction may be carried out, however wasteful existing methods might be.[11] Given the preponderance of amide formations in industry we believe that this contribution may prove of value. The process relies on a weakly absorbing complex **3** between an amine **1** and tetrachloromethane (**2**) (Scheme 1). A key advantage of this process is that it both avoids the use of expensive and toxic transition metals. It can be run at gram scale and be driven using any visible light source, such as a mercury arc lap, blue LED and more importantly, the sun.



Scheme 1. Proposed use of amines **1** as precursors for acid activating agent **2** and nucleophile **5** to form amides **7**.

Lautenberger has shown that trimethylamine (TEA), and tetrachloromethane (CCl_4) give rise to a light absorbing charge-transfer complexes i.e. **3**.[12,13] Indeed, under our experimental conditions, addition of TEA to a solution containing CCl_4 in

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dichloromethane ([CCl_4]>>[TEA]) results in the formation of a new light absorbing species (See Figure 1a and the ESI), presumably the 1:1 TEA···CCl_4 complex. According to the concentration-dependent changes in the absorption spectrum, the formation constant of the complex is around 0.15 M^{-1}, i.e. a slightly endergonic association. While triethylamine can bind to only one molecule of CCl_4, addition of CCl_4 to excess TEA in dichloromethane ([CCl_4]<[TEA]) results in a more complex behavior, probably due to the formation of higher stoichiometry complexes at high TEA to CCl_4 ratios. Gas-phase calculations (G4) on the trimethylamine (TMA) and CCl_4 system shows that the 1:1 TMA···CCl_4 complex is a minimum energy structure on the TMA + CCl_4 surface potential, with a **Cl-:N** distance of only 2.86 Å (Figure 1b). The calculated gas-phase thermodynamic parameters of the 1:1 complex are: $\Delta G°=+3.1$ $kcal \cdot mol^{-1}$, $\Delta H°=-3.7$ $kcal \cdot mol^{-1}$,$\Delta S°=-22.7$ $cal \cdot mol^{-1} \cdot K^{-1}$. The thermodynamic properties of the 1:1 TEA···CCl_4 complex, were extracted from the dependence of the association constant on temperature using a Van't Hoff plot. The complexation is indeed endergonic, $\Delta H°=+2.06\pm0.2$ $kcal \cdot mol^{-1}$, $\Delta S°=+4.1\pm0.8$ $cal \cdot mol^{-1} \cdot K^{-1}$, $\Delta G°=+0.9\pm0.45$ $kcal \cdot mol^{-1}$, (See Figure 2).

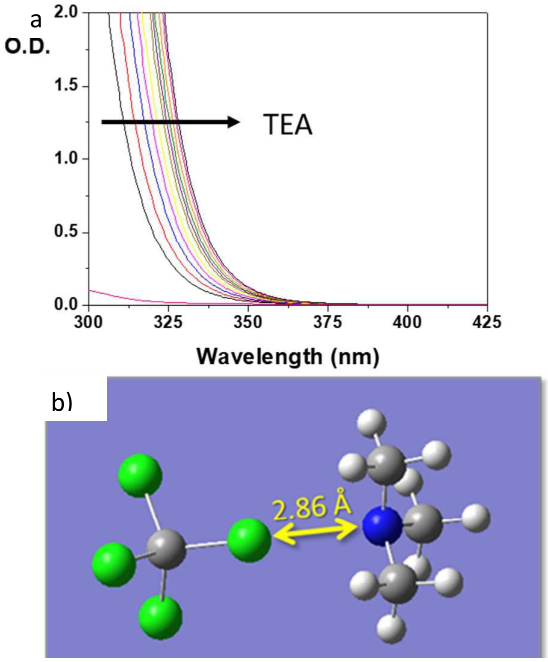

Fig. 1 a) UV-VIS spectra of a solution of 5.18 M CCl4 and increasing concentrations of TEA (0, 0.048, 0.072, 0.096, 0.119, 0.143, 0.167, 0.191, 0.215, 0.239, 0.263, 0.287 M) in DCM at 25±0.5 °C. b) Calculated structure (G4) of the TMA···CCl4 complex (trimethylamine is used as a model for TEA)..

Other tri-alkyl amines, such as tributylamine, were also found to form similar charge-transfer complexes with CCl_4 with similar absorption characteristics. However, mono-alkyl amines and di-alkyl amines, such as butylamine and dibutyl-amine, form considerably weaker complexes with CCl_4. These complexes absorb at shorter wavelengths (See ESI). These UV-VIS spectra show that while the charge-transfer complexes absorbs strongly in the UV part of the spectrum they still retain significant absorption in the near visible spectrum above 350 nm. In contrast, the absorption of both TEA and CCl_4 at >350 nm is negligible (See ESI). Based on this result, we envisioned the synthetic use of this complex in photoredox reactions assisted by sunlight while filtering off the UV section of the spectrum using the borosilicate glass walls of a the glass vessel as the filter (See ESI for filter properties). It should be noted that the use of amines in photocatalytic reactions has been reported previously.[1] In such reactions amines are oxidized by the light activated transition metal photocatalyst to form first cation radicals and then, after loss of a proton, iminium ions e.g. **4** (Scheme 1). The proposed scheme would achieve this in the absence of a transition metal catalyst.

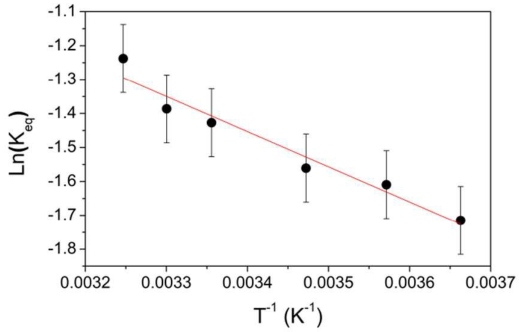

Fig. 2 Temperature dependence of the formation constant of the 1:1 TEA···CCl_4 complex.

Indeed, the irradiation of the charge-transfer complex using visible light led to the formation of iminium ion **4** (Scheme 1) as proven by ^1H and ^{13}C NMR (see ESI). We surmised that the incipient iminium ion **4** might react as both a dehydrating and activating agent **2** for the deprotonated carboxylic acid (Scheme 1). In this scheme the initially formed imininum ion **4** is attacked by the carboxylate **5** to give hemi-aminal ester **6**. Subsequent intramolecular attack on the electrophilic carbonyl function by either the amine of the aminal moiety, or through intermolecular attack by **7** (generated in the course of the reaction), leads to intermediate **8** or **9** respectively. Either intermediate would collapse to give the product amide **10** and one equivalent of aldehyde **11**. In the event of an intermolecular process a molecule of amine **7** would also be generated in the collapse of **9** to form **10** and **11**.

Thus, the overall dehydration would be divided into loss of oxygen from the carboxylic acid (to give aldehyde **11**) and loss of one proton from the amine and one proton from the carboxylic acid, thus requiring the use of at least two equivalents of base. A potential side-reaction was the possibility of decarboxylation of the carboxylic acid with loss of carbon dioxide via a radical pathway.

Consistent with our supposition, excitation of the charge-transfer complex **3** using LED as a source of visible light in the presence of benzoic acid in the presence of potassium carbonate (6.5 equiv.) under nitrogen led to formation of *N*,*N*-diethylbenzamide **10c** in 80% yield (Scheme 2). Importantly, carrying out the reaction using sunlight in a standard boro-silicate glass vessel, leads to the isolation of the product in

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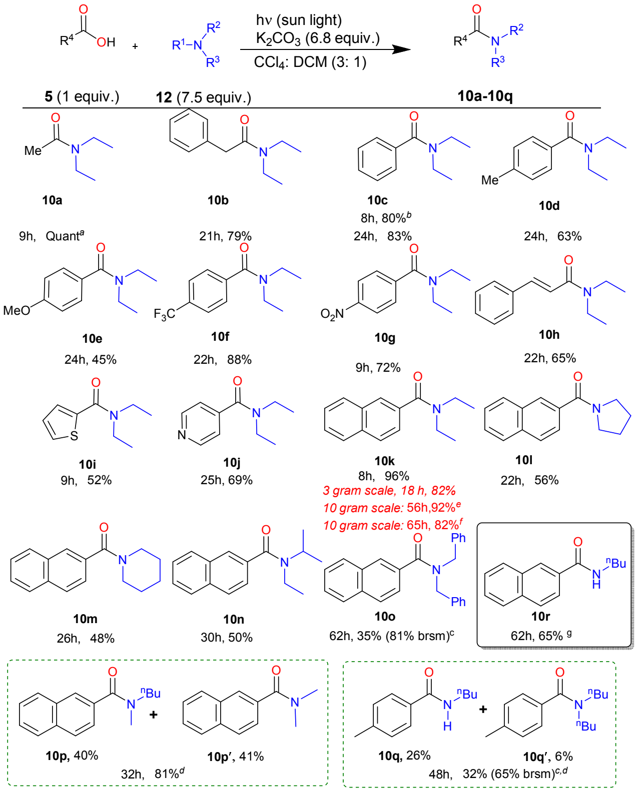
similar yield of 83% (Scheme 2, **10c**). While total light exposure was longer using sunlight (18h) than with LED (8h) it should be noted that the light flux for the LED was 55-65 mW/cm^2 compared to a light flux of 0.2 mW/cm^2 (early morning and late evening) up to 59 mW/cm^2 at noon using sun light.

Importantly, no reaction took place in the dark. The reaction is inhibited by oxygen, and does not produce product until oxygen is depleted. Accordingly, the optimized conditions include carrying out the reaction under an inert atmosphere. This observation is consistent with a mechanism in which the charge transfer complex **3** is converted into the iminium ion **4** and $CHCl_3$ (Scheme 1) through a free radical process. While the reaction requires an excess of amine (ca. 7 equiv.) for forming an efficient concentration of the complex, this component is inexpensive and may potentially be recycled. The finding that potassium carbonate is an essential additive was initially baffling as the excess of amine used ought to be sufficient to remove the two equivalents of acid generated in the reaction (Scheme 1). We surmise that the potassium carbonate acts primarily not as a base but as a dispersant and reflector of the incident light, and thus increases the light pathway through the reaction mixture many fold. Indeed, in its absence the rate of reaction drops significantly. 6.5 equivalents of regular commercial particle size appear to be the optimal quantity. Using smaller or higher amounts, or finer particle sizes, all lead to reduction of reaction rate.

Subsequently, the scope of the reaction was examined. Alkyl carboxylic acids such as acetic acid and phenyl acetic acid react with triethylamine to afford the corresponding diethylamides **10a** and **10b** in quantitative and 79% yield respectively (Scheme 2). A variety of aromatic carboxylic acids and amines (Scheme 2, **10c**-**10q**) are also substrates for the reaction. The yields in these reactions range from 52% for 2-thiophenylcarboxylic acid (**10i**) and up to 96% for 2-napthoic acid (**10k**). Benzoic acids substituted by electron-withdrawing groups are excellent substrates for the reaction. Thus, *para*-trifluorobenzoic acid affords the respective amide with triethylamine in 88% yield (**10f**) and *para*-Nitro-benzoic acid reacts with triethylamine to afford the corresponding diethyl-amide **10g** in 72% yield. Electron donating substituted aromatic acids also undergo the amidation reaction, albeit in slighter lower yield: 45 % (Scheme 2, **10e**).

The reaction is not limited to triethylamine. A variety of unsymmetrically substituted linear and cyclic alkylamines also lead to amide formation with 2-napthoic acid (Scheme 2, **10l**-**10q**). The reaction with dimethyl-butylamine leads to formation of a 1:1 mixture of demethylated (**10p**) and debutylated(**10p')** products in a combined 81% yield. The ratio, which contradicts the 2:1 ratio favoring **10p** expected on statistics, presumably reflects the higher stability of the more substituted N-butylidene-N-methylmethanaminium ion over the less substituted N-methyl-N-methylenebutan-1-aminium ion. It is therefore surprising that both methyl-pyrrolidine and methyl-piperidine lead to formation of the corresponding pyrrolidine and piperidine amides in 56% and 48% yields respectively (**10l** and **10m**) rather than suffering ring-opening to a greater extent. Notably, even highly hindered diisopropylethylamine (Hünig's base) could be used in the reaction as well, leading to formation of the hindered and challenging to make ethyl-isopropyl-amide of 2-napthoic carboxylic acid (**10n**).



Scheme 2. Reaction scope and general conditions. All the reactions were performed under N_2. Reaction times are given in parenthes, and refer to total sunlight exposure only. Products were isolated by column chromatography. Yields are given for isolated products unless otherwise indicated. [a] Conversion by HPLC. [b] Using an LED as the light source. [c] 57% 2-naphthoic acid and 51% 4-Methylbenzoic acid were recovered respectively. [d] Combined yields of products. [e] K_2CO_3 filtered of and replaced twice during the reaction. [f] with mechanical stirring at 85% conversion as determined by NMR. [g] Preliminary work: 7 equiv. DABCO, 1 equiv. Acid and 1.5 eequiv. N-butyl-amine. Yield determined at 80% conversion.

The reaction of dibutyl amine with 4-methylbenzoic acid (Scheme 2) while not of practical synthetic interest due to the very low absorbance of the dibutylamine-CCl_4 complex above 350 nm (See ESI) provides additional clues to the mechanistic understanding of the reaction. In this reaction the butyl amide **10q** and dibutyl amide **10q'** products were isolated in ca. 4:1 ratio in a combined 32% yield. Clearly, the dibutylamide **10q'** can only be formed via an intermolecular process (Scheme 1). In contrast, methyl-butylamide **10q** could in principle form through either an intramolecular or an intermolecular process. However, the intermolecular process can only take place after mono-butylamine is generated during the first cycle of the reaction. Initially butyl-amine would be present at very low concentration. In kinetic studies we do not observe an induction lag in product formation. Thus it is likely that amide formation takes place through both the intermolecular and intramolecular mechanisms proposed in Scheme 1.

Further support of the mechanism proposed in Scheme 1 arose from the reaction of 2-napthoic acid with

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tribenzylamide. Extended irradiation (62 h total) with sunlight followed by water workup afforded the expected amide product **10p** in 35% yield (81% based on recovered starting material) as well as benzaldehyde in 162% isolated yield (based on the amount of tribenzylamine used). This shows how iminium ion may function as the dehydrating agent in the reaction.

The reaction can be scaled up to 3 and 10 grams scale. Thus carrying out the reaction of 2-naphotic acid and triethylamine could be carried out in a standard 2L vessel to afford the product **10k** on a 10 gram scale in 92% yield. This indicates the advantage of using a low absorbing light harvesting complex. While the irradiation time at 3 gram scale is twice that required at 650 mg scale, this is a result of other factors such as the heterogeneous conditions. Using a higher light absorbing complex the reaction time would have been extended by at least one order of magnitude. An issue on scaleup to 10 g is that the reflecting material K_2CO_3 is crushed by heavy magnets and that powdered reflector inhibits the reaction. Accordingly, potassium carbonate had to be removed twice during the reaction and replaced with fresh material. One potential solution is to use mechanical stirring which is less prone to crush the particles leading to 80% yield at 85% conversion after 65 hours. However, these are engineering issues and will therefore not be discussed further here. Notably the reaction is clean with only starting materials and product observed.

While only secondary and tertiary amines form charge-transfer complexes that absorb in the visible region, a preliminary experiment showed that a primary amine can form amides in the reaction by using DABCO as a sacrificial amine. This also makes it possible to reduce the amount of nucleophilic amine to 1.5 equivalent. Thus napthoic acid reacts with butylamine to afford amide **10r** in 65% unoptimized yield at 80% conversion. Clearly this new reaction has a different mechanism since DABCO cannot form imine and further studies on this new reaction will be reported at a later date.

In conclusion, we present here the principle of using charge transfer complexes between amines and CCl_4 to drive synthetic reactions. Proof of principle is achieved in an efficient LED or sunlight-driven dealkylative condensation of a variety of amines with carboxylic acids. The reaction can be run at gram scale. The procedure is operationally simple and the starting materials as well as the light sources are inexpensive and readily available. No expensive coupling reagents are needed and the excess reagents and solvents should be easily recyclable in an industrial setting. A mechanism has been proposed, in which iminium ion formation occurs through light activation of the charge transfer complex between amine and CCl_4. The iminium ion acts as a combined dehydrating agent and activator of the carboxylic acid. The mechanism is supported by extensive experimental studies, and computations support the proposed key charge-transfer complex. The principles outlined herein are currently finding applications in other settings in our laboratory, the results of which will be reported in due course.

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