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# Light-enabled Synthesis of Anhydrides and Amides

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**ABSTRACT:** Recently, we have demonstrated that the photogeneration of Vilsmeier-Haack reagents are possible using only dimethylformamide (DMF) and tetrabromomethane (CBr<sub>4</sub>), in the bromination of alcohols. Extending these findings to carboxylic acid substrates has produced a mild and facile approach to the *in situ* formation of symmetric anhydrides, which were conveniently converted to amide derivatives in a one-pot process. The efficient protocols discussed herein are marked by use of UVA LEDs (365 nm) which have reduced reaction times and come with a low setup cost.

The activation of carboxylic acids has been paramount to the synthesis of peptides in coupling reactions with amines.<sup>1</sup> A variety of methods make carboxylic acids more electrophilic either by transforming the carboxylic acid into the corresponding acyl halide, or through the addition of coupling agents.<sup>2</sup> Symmetric anhydrides have also seen great use in peptide chemistry as they provide electrophilic activation of the carboxylic moiety without forming coupling by-products, as both electrophilic sites are identical. However, these anhydrides are often formed through the same procedures that apply to the amide couplings<sup>3</sup> (acyl halide formation and then addition of carboxylates). New protocols offering the formation of anhydrides directly from the corresponding carboxylic acids along with the direct formation of amides in a one-pot process are of interest for development.<sup>4</sup>

Photoredox catalysis has emerged as a powerful tool in the development of new organic transformations, especially in forming C-C, C-N, and C-O bonds.<sup>5</sup> Vilsmeier-Haack reagents for useful organic transformations can be generated with photoredox catalysis,<sup>6,7</sup> however, studies among our group found that generation of the *Vilsmeier-Haack reagent without use of a photocatalyst* is possible from the irradiation of CBr<sub>4</sub> with UVA light (365 nm LED) in DMF under air atmosphere.<sup>8</sup> Notably, visible light in comparison was unable to achieve this transformation. This was used as a synthetically facile route to bromoalkanes from alcohols, which was applicable to a one-pot deoxygenation protocol.<sup>8b,9</sup> Taking this into consideration, we sought to apply the photogeneration of Vilsmeier-Haack reagents from UVA and CBr<sub>4</sub> in a one-pot protocol for the synthesis of amides from readily available carboxylic acids and amines.

The formation of symmetric anhydrides was first optimized in order to minimize reagents used (Table 1). Treating *p*-anisic acid with one equivalent of  $CBr_4$  and two equivalents of 2,4,6-trimethylpyridine (collidine) in DMF were the conditions that gave anhydride product in the most reagent minimizing protocol, among the best yields (entries 1-3). The reaction was found to occur quickly, within 30 minutes, as indicated by the precipitation of collidine hydrobromide. Removal of collidine resulted in little product formation (entry 4). Control experiments were performed which demonstrated that no reaction oc-

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curred upon heating to  $80^{\circ}$ C without light irradiation in presence of CBr<sub>4</sub> (entry 5) or UVA irradiation in the absence of CBr<sub>4</sub> (entry 7). Notably, the transformation does not react under visible light irradiation (410 nm LED, entry 6).

 Table 1. Optimization of symmetric anhydrides.

MeO	ОН <u>СВг4, coll</u> DMF, 0.5 365 nm Ll	idine h ED MeO 2	Pa OMe
Entry	CBr <sub>4</sub> (equiv.)	Collidine (equiv.)	(%) <sup>a</sup>
1	1.0	5.0	95
2	0.5	5.0	78
3	1.0	2.0	91
4	0.5		9
5	1.0	2.0	n.r. <sup>b</sup>
6	1.0	2.0	n.r. <sup>c</sup>
7		2.0	n.r.

<sup>*a*1</sup>H NMR yield with mesitylene as internal standard. <sup>*b*</sup>Without irradiation, 80 °C overnight. n.r. = no reaction. <sup>*c*</sup>Using visible light.

Having these conditions in hand, we established the scope of the transformation using a wide array of carboxylic acids (Table 2). Non-aromatic carboxylic acids including long chains, primary, secondary, and tertiary α-centers were converted in nearly quantitative yields, forming stable anhydrides **2b-d** and **2h** (entries 1-3 and 7). The reaction proved to be tolerant to alkenes and alkynes, the corresponding anhydrides **2d-f** were obtained in 75% to 98% yields (entries 4-6)

**Table 2.** Formation of symmetric anhydrides from carboxylic acids.<sup>a</sup>

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<sup>*a*</sup>General conditions: Carboxylic acid (1 equiv.), DMF (0.2 M), collidine (2 equiv.), and lastly CBr<sub>4</sub> (1 equiv.) added to screw top vial, sealed, irradiated for 0.5 h w/365 nm LED. <sup>*b*1</sup>H NMR yield with mesity-lene as standard. <sup>*c*</sup>1.0 g scale of benzoic acid in 150 mL cylindrical Pyrex vessel.

Interestingly, *N*-Boc and *N*-CBz protected L-alanine showed only degradation (entry 8) however, Cbz protected L-proline was fully converted to the corresponding anhydride 2j (entry 9).<sup>10</sup> This may be attributed instability of the anhydride formed. Various aromatic carboxylic acids were screened; a wide variety of functionality is tolerated in good yields, including OMe, *t*Bu, halides, CF<sub>3</sub>, naphthyl, and to some extent, ortho and meta substitution (entries 10-20 and 24). 2-Carboxylic acid substituted heterocycles thiophene 2v, furan 2w, and N-methylpyrrole 2x were also compatible with this method (entries 21-23). Phthalic acid also converted quantitatively to phthalic anhydride 2z (entry 25), in an intramolecular version of this transformation.

The method showed a robust general applicability; however isolation of many aromatic anhydrides resulted in some degradation or loss of product. Often, these compounds are used in amide couplings as the coupling partner for an amine. It was reasoned that a one-pot procedure for the coupling of these anhydrides to an amine should be developed to avoid degradation of the anhydride through work up steps. An optimization of the bases added to the reaction (Table 3) showed that three equivalents of carboxylic acid, five equivalents of collidine and one equivalent of DMAP furnished the best yield of amide formation (**3**) in the coupling of carboxylic acid **1c** and piperidine using CBr<sub>4</sub> with UVA LED light in DMF (entry 9). The analogous method using  $[Ru(bpy)_3](PF_6)_2$  (5 mol%) with visible light (CFL light) gave little formation of either anhydride or amide product, 9% (entry 11). More importantly, the same reaction without  $[Ru(bpy)_3](PF_6)_2$  gave a similar yield, 7% (entry 12). This may be due to the intensity of these lights being relatively weak compared to high powered LED systems. A high powered 410 nm LED was used, giving 12% yield with  $[Ru(bpy)_3](PF_6)_2$ , but also yielded 8% without the photocatalyst (entries 13 and 14). One aspect of using more powerful lighting sources is that background activation (reaction with light source in absence of photocatalyst, as shown in this study) may occur, *which circumvents the need for photoredox catalysts*. Also, the excited state of  $[Ru(bpy)_3](PF_6)_2$ , may be quenched by the amine in solution, which does not result in product forming pathways. For these reasons, a photo-mediated method for the combination of carboxylic acids with amines without a photocatalyst gives the best conditions for amide synthesis.

**Table 3.** Optimization of one-pot amide formation.

CBr <sub>4</sub> (1 equiv.) DMF, 365 nm LED, 0.5 h	
Base	(%) <sup>a</sup>
Collidine	22
DMAP	22
DABCO	16
Imidazole	6
Pyridine	10
DBU	5
DIPEA	11
Collidine	$27^b$
Collidine	61 <sup>b,c</sup> , 38 <sup>d</sup>
Collidine	11 <sup>b,e</sup>
2,6-Lutidine	9 <sup>f</sup>
2,6-Lutidine	$7^g$
	CBr <sub>4</sub> (1 equiv.), base (3 equiv.) DMF, 365 nm LED, 0.5 h Base Collidine DMAP DABCO Imidazole Pyridine DBU DIPEA Collidine Collidine Collidine 2,6-Lutidine 2,6-Lutidine

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13	2,6-Lutidine	12 <sup><i>h</i></sup>
14	2,6-Lutidine	$8^i$

<sup>a1</sup>H NMR yield with mesitylene as standard, based on amine. <sup>b</sup>1 equiv. DMAP added. <sup>c</sup>3 equiv. 1c, 5 equiv. collidine, 1.5 equiv. CBr<sub>4</sub>. <sup>d</sup>1.0 g scale of piperidine in 150 mL cylindrical Pyrex vessel using same equiv. as in entry 9. <sup>e</sup>3 equiv. piperidine, 5 equiv. collidine, yield based on carboxylic acid. <sup>f</sup>[Ru(bpy)<sub>3</sub>](PF<sub>6</sub>)<sub>2</sub> 5mol%, Ar degas, CFL light 97 h. <sup>g</sup>No photocatalyst, Ar degas, CFL light 97 h. <sup>h</sup>[Ru(bpy)<sub>3</sub>](PF<sub>6</sub>)<sub>2</sub> 5 mol%, Ar degas, 410 nm LED, 0.5 h. <sup>i</sup>No photocatalyst, Ar degas, 410 nm LED, 0.5 h. <sup>i</sup>No photocatalyst, Ar degas, 410 nm LED, 0.5 h.

An extension of the amide protocol also showed promising results, (Table 4). Carboxylic acids functionalized with cyclohexane, phenyl, and 4-CF<sub>3</sub>-phenyl were chosen to represent alkyl, aryl, and electron withdrawing functionality. These were matched with *n*-butylamine, piperidine and aniline to represent primary, secondary and aromatic amines. Couplings of these compounds all proceeded in yields ranging from 34 to 98%. Interestingly, the examples using 4-CF<sub>3</sub>-benzoic acid for amide couplings obtained much higher yields of the amide products **4f-h** (entries 6-8) as compared to the isolation corresponding anhydride **2n** (*cf.* Table 2, entry 14). Benzoic acid was coupled with L-ala-OMe, which showed that amino acid derivatives **4i** retain their configuration throughout the reaction with 99:1 e.r. (entry 9), where racemization plagues many protocols.<sup>11</sup> Using *N*-Cbz-L-ala as carboxylic acid coupled with *n*-butylamine, conservation of enantiopurity was also observed with e.r. = 99:1, in 92% yield (entry 10). Coupling of L-ala-OMe and *N*-Cbz-L-ala as carboxylic acid demonstrated that the chirality of both centres are retained with d.r. >20:1, in 94% yield.

 Table 4. One-pot amidation protocol.



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Entry	R	N(R')R"	Product (yield %) <sup><math>a</math></sup>
1	Су	<i>n</i> -BuNH <sub>2</sub>	<b>4a</b> (98)
2	Су	PhNH <sub>2</sub>	<b>4b</b> (63)
3	Ph	piperidine	<b>4c</b> (80)
4	Ph	<i>n</i> -BuNH <sub>2</sub>	<b>4d</b> (86)
5	Ph	PhNH <sub>2</sub>	<b>4e</b> (75)
6	4-CF <sub>3</sub> Ph	piperidine	<b>4f</b> (90)
7	4-CF <sub>3</sub> Ph	<i>n</i> -BuNH <sub>2</sub>	<b>4g</b> (98)
8	4-CF <sub>3</sub> Ph	PhNH <sub>2</sub>	<b>4h</b> (94)
9	Ph	L-ala-OMe	<b>4i</b> $(34)^b$
10	N-Cbz-L-ala	<i>n</i> -BuNH <sub>2</sub>	<b>4j</b> (92) <sup>b</sup>
11	N-Cbz-L-ala	L-ala-OMe	<b>4k</b> $(94)^c$

<sup>*a*</sup>Isolated yield, based on amine. <sup>*b*</sup>e.r. = 99:1. <sup>*c*</sup>d.r. = >20:1 determined by <sup>1</sup>H NMR analysis.

Mechanistic consideration of this transformation is described in Scheme 1. Irradiation of CBr<sub>4</sub> produces an electrophilic radical CBr<sub>3</sub> which, upon addition to DMF, generates the radical intermediate **5**. Under these reaction conditions, **5** is readily oxidized to produce the Vilsmeier-Haack reagents **6** or .<sup>6-8</sup> In the presence of carboxylic acid, the latter is converted to intermediate **8**. At this point, intermediate **8** can be converted to corresponding anhydride **2** or amide **4**. The formation of amide **4** through a transient anhydride intermediate **2** could be also considered.



Scheme 1. Proposed Mechanism.

In summary, the photogeneration of Vilsmeier-Haack reagents from irradiation of CBr<sub>4</sub> with UVA light in DMF has been shown to be a useful method for the generation of symmetric anhydrides. This process is conveniently applicable to a one-pot synthesis of amides from readily available carboxylic acids and amines, without need of a photoredox catalyst. These studies not only exhibit the importance of photochemical transformations in the synthesis of amide bonds but also the power of conducting control reactions and light-source optimization in developing fast, efficient, and reagent minimizing methods in organic synthesis.

#### **Experimental Section**

**General Information.** All reactions were performed under atmospheric air (unless otherwise noted) in Pyrex glassware equipped with a magnetic stir bar, capped with a septum. DMF was filtered using a purification system. Commercial reagents were used without further purification. Reactions were monitored by thin layer chromatography (TLC) analysis. TLC plates were viewed under UV light and stained with potassium permanganate or p-anisaldehyde staining solution. <sup>1</sup>H NMR spectra were recorded on 300 MHz or 400 MHz in chloroform-d and chemical shifts are reported in ppm referenced to residual undeuterated solvent. Data are reported as follows: chemical shift, multiplicity, coupling, integration. <sup>13</sup>C NMR spectra were recorded on 75 MHz or 101 MHz. Optical rotations were recorded at 589 nm with 0.1 dm/2 mL sample cell. Retention of configuration was determined by running an analogous reaction with racemic mixtures of either amine or acid with respect to the amide couplings, with work-up in the usual way. Samples were diluted with 5% iPrOH in hexane, and run on a chiral HPLC, chromatographs available in the supporting information (column: AD-H, 5%iPrOH/Hexanes, 1.0 mL/min, over 60 minutes).

**General Procedure 1 (GP1).** *Preparation of symmetric anhydrides from carboxylic acids.* To an 8 mL pyrex screw-top reaction vessel was added substrate (0.3 mmol, 1.0 equiv.), Dimethylformamide (1.5 mL, 0.2 M), then 2,4,6-trimethylpyridine (0.6 mmol, 2.0 equiv.) and carbontetrabromide (0.3 mmol, 1.0 equiv.). The reaction mixture was capped and irradiated with a UVA (365 nm) LED at a distance of a centimetre, for 30 minutes. The resulting mixture was poured into a separatory funnel containing 25 mL of a 3:1 mixture of diethyl ether and hexanes (ethyl acetate added for compounds which needed further solubility). This was washed with water, where the combined aqueous fractions were re-extracted with 25 mL of diethyl ether. The combined organic portions were washed with saturated sodium bicarbonate, brine, and dried over sodium sulfate. The solution was concentrated in vacuo and products were weighed for crude yields and then were added an internal standard (mesitylene), where yields were determined with proton NMR by comparison to literature precedence.

**General Procedure 2 (GP2).** *Preparation of amides from carboxylic acids and amines.* To an 8 mL pyrex screw-top reaction vessel was added carboxylic acid (0.6 mmol, 3.0 equiv.), amine, (0.2 mmol, 1.0 equiv.), Dimethylformamide (1.0 mL, 0.2 M), then 2,4,6-trimethylpyridine (1.0 mmol, 5.0 equiv.), DMAP (0.2 mmol, 1.0 equiv.), and carbontetrabromide (0.3 mmol, 1.5 equiv.). The reaction mixture was capped and irradiated with a UVA (365 nm) LED at a distance of one cm, for 30 minutes. The resulting mixture was poured into a separatory funnel containing 25 mL of ethyl acetate. This was washed with 1 M HCl, where the combined aqueous fractions were re-extracted with 25 mL of ethyl acetate.

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The combined organic portions were washed with saturated sodium bicarbonate, brine, and dried over sodium sulfate. Products were further purified by column chromatography (0-100% EtOAc:Hex), relevant fractions combined, concentrated in vacuo, and characterized by NMR by comparison to literature precedence.

Compounds **2a-g** and **2k-z** were synthesized according to GP1 and characterized by NMR comparison.<sup>12</sup> Compounds **3**, **4a-k** were synthesized according to GP2 and characterized by NMR comparison.<sup>12</sup>

4-(3,4-dimethoxyphenyl)butanoic anhydride (2h): Synthesized according to GP1.

IR (neat, cm<sup>-1</sup>): 2933(m), 2836(w), 1813(s), 1745(s), 1648(m), 1591(s), 1514(vs), 1450(s), 1416(s). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  = 6.82 - 6.75 (m, 2 H), 6.75 - 6.65 (m, 4 H), 3.87 (s, 6 H), 3.85 (s, 6 H), 2.63 (t, *J*=7.5 Hz, 4 H), 2.44 (t, *J*=7.3 Hz, 4 H), 1.97 (quint, *J*=7.4 Hz, 4 H) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  = 169.2 (2 X C), 148.8 (2 X C), 147.3 (2 X C), 133.4 (2 X C), 120.2 (2 X CH), 111.6 (2 X CH), 111.2 (2 X CH), 55.8 (2 X CH<sub>3</sub>), 55.7 (2 X CH<sub>3</sub>), 34.2 (2 X CH<sub>2</sub>), 34.2 (2 X CH<sub>2</sub>), 25.8 (2 X CH<sub>2</sub>) ppm. HRMS (EI) m/z calcd for C<sub>24</sub>H<sub>30</sub>O<sub>7</sub> [M<sup>+</sup>] 430.1992, found 430.1993.

(R)-1-((benzyloxy)carbonyl)pyrrolidine-2-carboxylic anhydride (2j): Synthesized according to GP1.

IR (neat, cm<sup>-1</sup>): 2995(m), 2882(w), 1827(s), 1745(s), 1697(vs) (overlapping), 1411(s), 1352(vs). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): **δ** = 7.45 - 7.23 (m, 10 H), 5.25 - 5.03 (m, 4 H), 4.51 - 4.28 (m, 2 H), 3.72 -3.42 (m, 4 H), 2.22 - 1.84 (m, 8 H) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): **δ** = 167.7, 167.6, 167.5, 167.4 (2 X C, rotamers), 155.9, 154.8, 154.6, 153.9 (2 X C, rotamers), 136.8, 136.6, 136.4, 136.2 (2 X C, rotamers), 128.4, 128.4, 128.2, 128.0, 128.0, 127.9, 127.9, 127.8, 127.7, 127.5, 127.4 (10 X CH, rotamers), 67.3, 67.3, 67.2, 67.1 (2 X CH<sub>2</sub>, rotamers), 59.7, 59.6, 59.3, 59.2 (2 X CH, rotamers), 46.9, 46.9, 46.4, 46.3 (2 X CH<sub>2</sub>, rotamers), 31.0, 30.2, 30.2, 30.1, 29.6, 29.5, 29.0, 28.9 (2 X CH<sub>2</sub>, rotamers), 24.2, 24.2, 23.4, 23.3 (2 X CH<sub>2</sub>, rotamers) ppm. HRMS (EI) m/z calcd for  $C_{26}H_{28}N_2O_7$  [M<sup>+</sup>] 480.1897, found product was unstable. [ $\alpha$ ]<sup>20</sup><sub>D</sub> = -32.1° (c 1.0, EtOH).

*methyl benzoyl-L-alaninate (4i):* Synthesized according to GP2 and characterized according to NMR comparison.<sup>12</sup>  $[\alpha]^{20}{}_{D} = +30.2^{\circ}$  (c 1.0, CHCl<sub>3</sub>).

*benzyl (S)-(1-(butylamino)-1-oxopropan-2-yl)carbamate (4j):* Synthesized according to GP2 and characterized according to NMR comparison.<sup>12</sup>  $[\alpha]^{20}_{D} = -6.8^{\circ}$  (c 1.0, EtOH).

*Z-L-ala-L-ala-OMe (4k):* Synthesized according to GP2 and characterized according to NMR comparison.<sup>12</sup>  $\left[\alpha\right]^{20}_{D} = -49.0^{\circ}$  (c 1.0, MeOH).

# **Supporting Information**

Chiral-HPLC data for hydrolysis of **2j** yielding Z-L-proline and compounds **4i-k** along with <sup>1</sup>H NMR and <sup>13</sup>C NMR for compounds **2h**, **2j**, **3** and **4a-k**. This material is available free of charge via the Internet at <u>http://pubs.acs.org/</u>

### **Author Information**

#### **Author Contributions**

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

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