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Visible-Light-Mediated Aerobic Oxidative $C(sp^3)$ - $C(sp^3)$ Bond Cleavage of Morpholine Derivatives Using 4CzIPN as a Photocatalyst

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Abstract. Herein, a metal-free strategy for the aerobic oxidative cleavage of the inert $C(sp^3)$ – $C(sp^3)$ bond was developed. Deconstruction of morpholine derivatives was conducted using visible light as an energy source and O₂ as an oxidant under mild conditions. This procedure demonstrated suitable selectivity and functional group tolerance. Moreover, a possible mechanism involving a radical process was proposed based on a series of mechanism exploration and control experiments.

Keywords: C–C bond cleavage; 4CzIPN; morpholine derivatives; photocatalysis; radical

Introduction

As a means of selective deconstruction and functionalization, the cleavage of C-C bonds is of considerable significance in organic synthesis and medicinal chemistry,^[1] because it provides a complementary strategy the for activation/functionalization of $C(sp^3)$ - $C(sp^3)$ during the construction of complex molecules.^[2] However, selective cleavage of the C-C bond under mild conditions remains a huge challenge due to the inherent characteristics, such as high bond dissociation energy (~90 kcal/mol), non-polarity, and kinetic inertness of this bond.^[3] Therefore, the cleavage of C-C bonds is commonly achieved by releasing the strain in three- or four-membered rings; nevertheless, relatively few studies have been reported on the cleavage of C-C bonds in unstrained molecules, specifically under mild and metal-free conditions. In recent years, substantial efforts have been made to develop methods for the cleavage of inert C-C bonds;^[4] among these methods, direct oxidative addition,^[5] β -carbon elimination,^[6] retro-allylation,^[7] and cross-alkane metathesis^[8] have been mostly used. Notably, hazardous oxidants $(O_3, [^{9a]}$ tert-butyl hydroperoxide, $[^{9b]}$ NaIO₄, $[^{9c-9d]}$ and Pb(OAc)4^[9e]) or relatively harsh reaction conditions (such as elevated temperatures and high pressures)^[10] are typically needed for the oxidative cleavage of C–C bonds, which limit the application of this strategy. Therefore, exploring effective methods for the oxidative cleavage of C–C bonds under mild conditions is highly required.

Morpholine moieties are widely used in drugs and bioactive molecules owing to their advantageous physicochemical, biological, and metaboli properties.^[11] Among the top 200 pharmaceuticals by retail sales in 2019, there are five drugs (namely, Xarelto, Genvoya, Prezista, Kyprolis, and Alecensa) containing morpholine moieties.^[12] Considering the importance of morpholine in the field of medicine, studying the C-C cleavage of morpholine is of considerable importance to the research of drug metabolites. Additionally, multifunctional compounds can be obtained by cleaving the C-C bond of morpholine derivatives, which are highly valuable in organic synthesis.

2008. discovered In Albini et al. that morpholinofluorophenyloxazolidinone irradiated with ultraviolet (UV) light (310 nm) in N₂-flushed water yielded the corresponding ring-opening product in only a small amount, as indicated by high-performance liquid chromatography/mass spectrometry (Scheme 1(a)).^[13] In 2012, Bruschi et al. reported the oxidative cleavage of morpholine derivatives by O_3 ; however, the yield of the desired ring-opening product was only 17% (Scheme 1(b)).^[14] In 2019, Beller et al. developed a protocol for the aerobic cleavage of the C-C bond using a Cu catalyst or Co-Mn catalyst (Scheme 1(c)).^[15] Although oxidative cleavage of the morpholine ring has been successfully achieved via these methods, the application of these methods is hindered by the low yield of products or the requirement of harsh conditions, including high temperatures and pressures. Considering the importance of preparing drug metabolites or potential metabolites via the selective cleavage of C-C bonds in the later stage^[16] and the strict restrictions on the levels of residual heavy metals in the pharmaceutical industry,^[17] the establishment of metal-free and mild strategies is necessary to realize the oxidative cleavage of morpholine.

Visible-light catalysis is a green and sustainable method for constructing complex molecules under mild conditions and has been extensively used for C-C bond cleavage.^[18] Inspired by related previous studies and our continuous interest in visible-light catalysis,^[19] we proposed that photoredox catalysis might be a mild and feasible method for the oxidative cleavage of morpholine. Herein, we report a visiblelight-mediated C-C bond cleavage of morpholine derivatives for the synthesis 2-(Nof arylformamido)ethyl formates (Scheme 1(d)) using O₂ as an oxidant and the organic dye 2,4,5,6tetrakis(carbazol-9-yl)-1,3-dicyanobenzene (4CzIPN) as a photocatalyst; this strategy does not require the use of transition metals and (over) stoichiometric oxidants and has broad substrate applicability. This reaction affords a mild approach for the aerobic cleavage of the unstrained $C(sp^3)$ – $C(sp^3)$ bond.



Scheme 1. Oxidative cleavage of morpholine derivatives.

Results and Discussion

In our preliminary study, 4-phenylmorpholine (1a) was selected as a model substrate. We initially conducted the reaction using different photocatalysts (1 mol%) in N,N-dimethylformamide (DMF) under irradiation of 9 W blue light-emitting diodes (LEDs) and an O₂ atmosphere at room temperature for 24 h [Supporting Information (SI), Table S1]. The reactions performed using [Ir(dtbbpy)(ppy)₂][PF₆] and 4CzIPN afforded the desired product 1b in acceptable yields (59 and 61%, respectively). Considering the problem of metal residues and the potential hazards of transition metals,^[16] we chose 4CzIPN as the photocatalyst. Subsequently, we conducted a solvent screening, and the results suggested that acetonitrile (MeCN) was a more suitable solvent for this reaction (SI, Table S2). To determine better reaction conditions, photocatalyst loading, light source, and additives were separately analyzed (SI, Tables S3–S6). Finally, 1b was acquired in 75% yield under the following optimal conditions (SI, Table S6, entry 3): substrate: 1a (0.3 mmol, 1.0 equiv.); photocatalyst: 4CzIPN (1 mol%); additive: 2,6-lutidine (1.0 equiv.); solvent: MeCN; irradiation source: 9 W blue LEDs; atmosphere: O2 (O2 balloon); and room temperature.

After determining the optimal conditions, we studied a series of substituted morpholines to reveal the substrate scope of the reaction (Schemes 2 and 3). At first, the influence of the N-substituents of morpholine on the reaction was investigated (Scheme 2). N-Phenylmorpholines with different substituents (-Cl, -Br, -CN, and -COMe) on the phenyl moiety performed well in the reaction, providing the desired. products 3b-10b in moderate yields. N-Phenylmorpholine with a methyl group at the orth position of the N-phenyl moiety afforded 2b in a lower yield than that of 11b acquired using N phenylmorpholine with a methyl group at the para position; this might be due to steric hindrance. However, when 4-(4-methoxyphenyl)morpholine (12a) was used in our reaction system, 12b could only be obtained in 20% yield, and most of the starting material remained unchanged (conversion: 30%). The carboxyl group was also tolerated in this reaction, where 70% of the starting material was converted and 54% 13b was acquired. In this case, 2 mL MeCN was used as a solvent to dissolve the substrate. Substrates with disubstituted electron-withdrawing or electrondonating groups on the *N*-phenyl moiety underwent smooth oxidative cleavage (14b–16b). When 4-(3,5dichlorophenyl)morpholine (14a) was employed as a substrate, the expected product 14b was achieved in 59% yield, and its corresponding hydrolysate (14c) was obtained in 13% yield. To our delight, when the *N*-groups on the morpholine moiety were changed to biphenyl, pyridyl, and benzoheterocycles, the corresponding products 17b-21b were acquired in satisfactory yields.

Scheme 2. Evaluation of the substrate scope by variation in the *N*-substituents of morpholine^a



^aUnless otherwise stated, the following conditions were used: **a** (0.3 mmol, 1.0 equiv.), 4CzIPN (1 mol%), and 2,6lutidine (1 equiv.) in MeCN (1 mL) irradiated with 9 W blue LEDs at room temperature under an O₂ atmosphere (O₂ balloon) for 24 h. Isolated yield. ^b2 mL MeCN as the solvent. ^cDMF as the solvent.

Subsequently, the scope of substituted morpholines (Scheme 3). was explored **Ring-substituted** morpholines were also reactive in our reaction system and yielded the desired products 22b-29b in 52-83% yields. Note that the methyl group at the C3 position of the morpholine ring exclusively led to the oxidative cleavage of the unsubstituted C-C bond (22b), whereas the methyl group at the C2 position resulted in the selective cleavage of the C5-C6 bond vs. the C2–C3 bond (3:2) (23b and 23b', respectively). For low-yield substrates, the lactams \mathbf{g} and the alcohol compounds c were detected as the main by-products (SI, Scheme S3). In addition to morpholine derivatives, 1-phenylpiperidine (**1d**) underwent а similar transformation and produced the oxidative product 1e in 47% yield, which could not be achieved in Beller's study.^[15] However, when the tertiary amine 2d was employed in the reaction, most of the starting material remained unchanged, and the dealkylated product 2f was obtained in 19% yield possibly owing to the hydrolysis of the imine ion intermediate formed during photocatalysis.^[20] To test the tolerance of this protocol to N-alkyl groups, the reactions of N-benzyl and Ncyclohexyl morpholines were conducted under the standard conditions. Nevertheless, the cleavage products of the C-N bond between the N and alkyl groups were acquired instead of the cleavage product of the C–C bond of the morpholine ring.^[21]

Scheme 3. Substrate scope of ring-substituted morpholines and tertiary amines^a



^aUnless otherwise stated, the following conditions were employed: **a** (0.3 mmol, 1.0 equiv.), 4CzIPN (1 mol%), and 2,6-lutidine (1 equiv.) in MeCN (1 mL) irradiated with 9 W blue LEDs at room temperature under an O_2 atmosphere (O_2 balloon) for 24 h. Isolated yield.

Additionally, **1b** was easily hydrolyzed to *N*-arylamino alcohol (**1c**) in excellent yield under basic conditions (Scheme 4), which is a useful synthon it. organic synthesis.





^aReaction conditions: to a solution of **1b** (1.0 mmol) in MeOH (4.1 mL), NaOH (5 mol/L) was added to achieve a mixture with pH = 12.0, and then, the mixture was stirred at 55 °C (oil bath) for 12 h.

To gain some insight into this visible-light photoredox catalysis, few control experiments were performed (Table 1). Results revealed that both visible light and the photocatalyst played an indispensable role in the reaction because no product was detected when the reaction was executed without one of them (Table 1, entries 2 and 3). Moreover, when the reaction was conducted under an Ar atmosphere instead of an O₂ atmosphere, only a trace amount of **1b** was acquired (Table 1, entry 4), indicating that O_2 was required for this reaction. When 2.0 equiv. of radical scavengers (namely, 2,2,6,6-tetramethylpiperidinooxy (TEMPO) and 2,6-di-tert-butyl-4-methylphenol (BHT) were added to the reaction system, 1b was not obtained (Scheme 5(a) and (b), respectively), suggesting that the reaction might involve a radical process. Subsequently, fluorescence quenching experiments, cyclic voltammetry (CV), and light/dark experiments were performed to further understand the reaction

mechanism. Fluorescence quenching experiments showed that 1a effectively quenched the excited photocatalyst 4CzIPN* (SI, Figures S1 and S2). The oxidation potential of 1a (E_{ox} = +1.030 V vs. saturated calomel electrode (SCE) in MeCN) (SI, Figure S4) measured by CV revealed that **1a** could be oxidized by 4CzIPN^* (E_{ox} = +1.35 V vs. SCE in MeCN)^[22] via a single-electron transfer (SET) process. To evaluate the role of 2.6-lutidine in the reaction, we also tested the oxidation potential of **1a** in the presence of 2,6-lutidine. Results showed that in the presence of 2,6-lutidine, the oxidation potential of **1a** decreased to +0.991 V vs. SCE in MeCN, implying that **1a** could be easily oxidized by 4CzIPN* (SI, Figure S4). Next, the light/dark experiments indicated that the yield of the reaction did not significantly increase under dark conditions (SI, Figure S5), and the quantum yield (Φ) experiments ($\Phi = 0.088$; for details, see SI) further proved that the reaction did not involve a radical chain propagation process. Additionally, to explore the source of the carbonyl O in the product, an ¹⁸O₂ labeling experiment was conducted (Scheme 5(c)). The model reaction was performed under an ¹⁸O₂ atmosphere (¹⁸O₂ balloon), and ¹⁸O was detected in the product by resulting high-resolution mass spectrometry (HRMS), suggesting that O₂ was the source of the carbonyl O.

To verify whether the reaction included singlet oxygen $({}^{1}O_{2})$, we conducted some experiments. Fluorescence quenching experiments of 4CzIPN* with O₂ and Ar were performed in MeCN (SI, Figure S3), which showed that O₂ efficiently quenched 4CzIPN*. Next, when the ${}^{1}O_{2}$ inhibitor β -carotene (2.0 equiv.) was introduced into the model reaction system, 1b was not achieved (Scheme 5(d)), suggesting that the reaction might involve ¹O₂. Considering that ¹O₂ can be easily added to double bonds to form dioxetane,^[23] we speculate that the reaction may involve an enamine intermediate. To detect the existence of the enamine intermediate, the model reaction was executed under standard conditions, and a small amount of reaction mixture was withdrawn after 11 h for HRMS. The enamine intermediate V was discovered by HRMS (Scheme 5(e) and Figure S9).





^aUnless otherwise stated, the following conditions were used: **1a** (0.3 mmol, 1.0 equiv.), 4CzIPN (1 mol%), and 2,6-lutidine (1 equiv.) in MeCN (1 mL) irradiated with 9 W blue LEDs at room temperature under an O_2 atmosphere (O_2 balloon) for 24 h. ^bIsolated yield.

Scheme 5. Mechanistic studies



Based on the above mentioned findings and previous studies,^[3d,23-27] a plausible mechanism was proposed (Scheme 6). Initially, 4CzIPN absorbs visible light and is converted to 4CzIPN*, which is reduced by N-aryl morpholine (a) via a SET process to produce the aminium radical cation I and 4CzIPN⁻. H abstraction occurs between I and superoxide anion (O_2^{\bullet}) (generated by the SET process between 4CzIPN⁻ and O₂ during the photoredox cycle^[24]) to provide an iminium intermediate (IV).[25] IV loses a proton and is transformed into an enamine (V). V reacts with ¹O₂ produced by sensitization with 4CzIPN* via energy transfer (ET) to yield the dioxetane intermediate VI.^[23] VI readily decomposes to afford the desired product **b**.^[26] In some cases, a small part of **b** is hydrolyzed into the by-product **c**.

In contrast, in the radical trapping experiments (Scheme 5(b)), the radical intermediate II and HOO• were detected by HRMS. Additionally, **g** was isolated in small amounts from several reactions. Thus, we hypothesize that a small amount of I may undergo deprotonation in the presence of O_2^{\bullet} . Subsequently, II is captured by HOO• to generate a peroxide (III), which is dehydrated to form **g**.^[27]

Scheme 6. Proposed mechanism



Conclusion

In summary, herein, we successfully developed a mild method for the aerobic cleavage of unstrained $C(sp^3)-C(sp^3)$ bonds using visible light as an energy source and O₂ as an oxidant. The reaction avoids the use of transition metals, elevated temperatures, high pressures, and dangerous stoichiometric oxidants. This procedure demonstrated the suitable tolerance of functional groups, and 31 products were obtained with yields of up to 83%; thus, this study provides an alternative approach for the oxidative cleavage of morpholine derivatives under mild conditions.

Experimental Section

General. Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. Reactions were monitored by thin-layer chromatography (TLC) with Haiyang GF 254 silica gel plates (Qingdao Haiyang chemical industry Co., Ltd., Qingdao, China) using UV light and vanillic aldehyde or phosphomolybdic acid as visualizing agents. Flash column chromatography was performed using 200–300 mesh silica gel under high pressures. ¹H nuclear magnetic resonance (NMR) and ¹⁵C NMR spectra were recorded via 600 MHz and 151 MHz NMR spectrometers, respectively. Chemical shifts (δ) were expressed in ppm with tetramethylsilane as an internal standard, and coupling constants (*J*) are reported in Hz. High-resolution mass spectra were acquired using electrospray ionization sources (quadrupole time-of-flight mass spectrometer, Bruker Impact II, Bremen, Germany). Melting points (m. p.) were evaluated using a melting point apparatus (WPX-4, Yice instrument equipment Co., Ltd., Shanghai) and were uncorrected. Furthermore, 9 W blue LEDs (Xinyuan Optoelectronics, LD-QP, rated power: 9 W, frequency: 50/60 Hz) were procured from Taobao.

General experimental procedure for the synthesis of b. A 10 mL round-bottom flask equipped with a stirring bar was charged with a (0.3 mmol, 1.0 equiv.), 4CzIPN (1 mol%), 2,6-lutidine (1 equiv.), and MeCN (1 mL). The mixture was stirred at room temperature under an O_2 atmosphere (O_2 balloon) and irradiated with 9 W blue LEDs (415–494 nm, Xinyuan Optoelectronics; the distance between light and the flask was approximately 4 cm) for 24 h. After completion of the reaction (detected by TLC), MeCN was removed from the reaction mixture. The residue was purified by flash chromatography on silica gel using petroleum ether/ethyl acetate (EtOAc) as the eluent to obtain **b**.

2-(N-Phenylformamido)ethyl formate (1b):^{15a} $R_f = 0.25$ (Petroleum ether:EtOAc = 3:1); 43.4 mg, 75% yield; light yellow liquid; ¹H NMR (600 MHz, Chloroform-*d*): δ 8.40

(s, 1H), 7.97 (s, 1H), 7.43 (t, J = 7.7 Hz, 2H), 7.33 (t, J = 7.4 Hz, 1H), 7.22 (d, J = 7.9 Hz, 2H), 4.34 (t, J = 5.6 Hz, 2H), 4.11 (t, J = 5.6 Hz, 2H); ¹³C NMR (151 MHz, Chloroform-d): δ 162.7, 160.6, 140.7, 129.8, 127.3, 124.5, 60.6, 44.2.

2-(Phenylamino)ethan-1-ol (1c):²⁸ $R_f = 0.25$ (Dichloromethane:Methanol = 50:1); 130.2 mg, 95% yield; colorless liquid; ¹H NMR (600 MHz, Dimethyl sulfoxide (DMSO)- d_6): δ 7.07–7.04 (m, 2H), 6.57 (d, J = 7.9 Hz, 2H), 6.51 (t, J = 7.2 Hz, 1H), 5.39 (t, J = 5.8 Hz, 1H), 4.66 (t, J = 5.5 Hz, 1H), 3.55 (q, J = 5.9 Hz, 2H), 3.08 (q, J = 5.9 Hz, 2H); ¹³C NMR (151 MHz, DMSO- d_6): δ 149.4, 129.3, 116.1, 112.5, 60.2, 46.1.

2-(N-o-Tolylformamido)ethyl formate (2b):^{15a} $R_f = 0.25$ (Petroleum ether:EtOAc = 2:1); 18.8 mg, 30% yield; light yellow liquid; ¹H NMR (600 MHz, Chloroform-*d*): δ 8.15 (s, 1H), 7.98 (s, 1H), 7.31–7.30 (m, 2H), 7.28–7.26 (m, 1H), 7.16 (d, *J* = 7.8 Hz, 1H), 4.30 (t, *J* = 5.6 Hz, 2H), 3.98 (t, *J* = 5.3 Hz, 2H), 2.27 (s, 3H); ¹³C NMR (151 MHz, Chloroform-*d*): δ 163.3, 160.5, 138.9, 135.8, 131.6, 128. 8, 128.8, 127.2, 60.6, 44.2, 17.7.

2-(N-(3-Chlorophenyl)formamido)ethyl formate (3b):^{15a} R_f = 0.25 (Petroleum ether:EtOAc = 3:1); 38.3 mg, 56% yield; light yellow liquid; ¹H NMR (600 MHz, Chloroform*d*): δ 8.41 (s, 1H), 7.99 (s, 1H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.32–7.30 (m, 1H), 7.25–7.23 (m, 1H), 7.12–7.10 (m, 1H), 4.35 (t, *J* = 5.5 Hz, 2H), 4.09 (t, *J* = 5.6 Hz, 2H); ¹³C NMR (151 MHz, Chloroform-*d*): δ 162.3, 160.5, 142.0, 135.5, 130.8, 127.4, 124.5, 122.3, 60.6, 44.3.

2-(*N*-(**3-Bromophenyl**)formamido)ethyl formate (4b):^{15a} $R_f = 0.25$ (Petroleum ether:EtOAc = 3:1); 49.4 mg, 61% yield; yellow liquid; ¹H NMR (600 MHz, Chloroform-*d*): δ 8.40 (s, 1H), 7.98 (s, 1H), 7.48–7.45 (m, 1H), 7.40–7.39 (m, 1H), 7.31 (t, *J* = 8.0 Hz, 1H), 7.17–7.15 (m, 1H), 4.35 (t, *J* = 5.6 Hz, 2H), 4.09 (t, *J* = 5.6 Hz, 2H); ¹³C NMR (151 MHz, Chloroform-*d*): δ 162.2, 160.4, 142.1, 131.1, 130.4, 127.4 123.3, 122.8, 60.6, 44.3.

2-(N-(3-Cyanophenyl)formamido)ethyl formate (5b):¹⁵ R_f = 0.25 (Petroleum ether:EtOAc = 2:1); 30.0 mg, 55% yield; light yellow liquid; ¹H NMR (600 MHz, Chloroform *d*): δ 8.45 (s, 1H), 7.99 (s, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.60–7.57 (m, 2H), 7.51 (d, *J* = 8.0 Hz, 1H), 4.38 (t, *J* = 5.5 Hz, 2H), 4.13 (t, *J* = 5.5 Hz, 2H); ¹³C NMR (151 MHz, Chloroform-*d*): δ 162.0, 160.4, 141.9, 130.9, 130.6, 128.3, 127.2, 117.6, 114.2, 60.6, 44.5.

2-(N-(3-Acetylphenyl)formamido)ethyl formate (6b):^{15a} R_f = 0.25 (Petroleum ether:EtOAc = 1.5:1); 37.4 mg, 53% yield; light yellow liquid; ¹H NMR (600 MHz, Chloroformd): δ 8.44 (s, 1H), 7.97 (s, 1H), 7.90–7.89 (m, 1H), 7.82 (t, J = 2.0 Hz, 1H), 7.57–7.54 (m, 1H), 7.44–7.42 (m, 1H), 4.35 (t, J = 5.5 Hz, 2H), 4.14 (t, J = 5.6 Hz, 2H), 2.63 (s, 3H); ¹³C NMR (151 MHz, Chloroform-d): δ 196.8, 162.3, 160.5, 141.3, 138.7, 130.2, 128.5, 127.1, 123.5, 60.6, 44.2, 26.6.

2-(N-(4-Chlorophenyl)formamido)ethyl formate (7b):^{15a} $R_f = 0.25$ (Petroleum ether:EtOAc = 3:1); 41.8 mg, 61% yield; light yellow liquid; ¹H NMR (600 MHz, Chloroform *d*): δ 8.37 (s, 1H), 7.97 (s, 1H), 7.41–7.39 (m, 2H), 7.17–7.15 (m, 2H), 4.34 (t, *J* = 5.6 Hz, 2H), 4.08 (t, *J* = 5.5 Hz, 2H); ¹³C NMR (151 MHz, Chloroform-*d*): δ 162.3, 160.5, 139.3, 133.1, 130.0, 125.7, 60.6, 44.4.

2-(*N*-(**4-Bromophenyl**)*formamido*)*ethyl formate* (**8***b*):^{15a} $R_f = 0.25$ (Petroleum ether:EtOAc = 3:1); 47.5 mg, 58% yield; yellow liquid; ¹H NMR (600 MHz, Chloroform-*d*): δ 8.37 (s, 1H), 7.97 (s, 1H), 7.56 (d, *J* = 8.6 Hz, 2H), 7.11 (d, *J* = 8.7 Hz, 2H), 4.34 (t, *J* = 5.6 Hz, 2H), 4.08 (t, *J* = 5.6 Hz, 2H); ¹³C NMR (151 MHz, Chloroform-*d*): δ 162.2, 160.4, 139.8, 133.0, 125.9, 120.8, 60.6, 44.3.

2-(N-(4-Cyanophenyl)formamido)ethyl formate (9b):^{15a} $R_f = 0.25$ (Petroleum ether:EtOAc = 3:1); 45.3 mg, 69% yield; light yellow solid; m. p.: 75–76 °C; ¹H NMR (600 MHz, Chloroform-*d*): δ 8.54 (s, 1H), 7.97 (s, 1H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), 4.39 (t, *J* = 5.5 Hz, 2H), 4.15 (t, *J* = 5.5 Hz, 2H); ¹³C NMR (151 MHz, Chloroform-*d*): δ 161.8, 160.4, 144.8, 133.9, 123.3, 117.9, 110.5 °C 6.4 4 110.5, 60.6, 44.1.

2-(*N*-(4-Acetylphenyl)formamido)ethyl formate (10b):^{15a} $R_f = 0.25$ (Petroleum ether:EtOAc = 1.5:1); 39.9 mg, 57% yield; light yellow liquid; ¹H NMR (600 MHz, formate Chloroform-*d*): δ 8.55 (s, 1H), 8.04 (d, *J* = 8.3 Hz, 2H), 7.97 (s, 1H), 7.32 (d, *J* = 8.3 Hz, 2H), 4.38 (t, *J* = 5.6 Hz, 2H), 4.17 (t, *J* = 5.6 Hz, 2H), 2.62 (s, 3H); ¹³C NMR (151 MHz, Chloroform-*d*): δ 196.6, 162.1, 160.4, 144.8, 135.4, 130.1, 122.8, 60.6, 64.20, 26.5 122.8, 60.6, 43.9, 26.5.

4-(4-Acetylphenyl)morpholin-3-one (10 g): $R_f = 0.25$ (Petroleum ether:EtOAc = 1:1); 4.0 mg, 6% yield; white solid; m. p.: 122–123 °C; ¹H NMR (600 MHz, Chloroform-*d*): δ 8.01 (d, J = 8.2 Hz, 2H), 7.50 (d, J = 8.2 Hz, 2H), 4.37 (s, 2H), 4.07–4.05 (m, 2H), 3.83–3.82 (m, 2H), 2.60 (s, 3H); ¹³C NMR (151 MHz, Chloroform-d): δ 197.0, 166.7, 145.4, 135.2, 129.4, 124.6, 68.6, 64.0, 49.1, 26.6; HRMS (ESI): m/z: calcd. for C₁₂H₁₃NO₃ (M+H)⁺: 220.0968; found: 220.0966.

2-(N-p-Tolylformamido)ethyl formate (11b): 15a R_f = 0.25 (Petroleum ether:EtOAc = 3:1); 42.2 mg, 68% yield; light yellow liquid; ¹H NMR (600 MHz, Chloroform-*d*): δ 8.35 (s, 1H), 7.98 (s, 1H), 7.22 (d, *J* = 7.8 Hz, 2H), 7.09 (d, *J* = 8.3 Hz, 2H), 4.32 (t, *J* = 5.7 Hz, 2H), 4.07 (t, *J* = 5.7 Hz, 2H), 2.37 (s, 3H); ¹³C NMR (151 MHz, Chloroform-*d*): δ 162.7, 160.6, 138.1, 137.4, 130.4, 124.7, 60.6, 44.3, 20.9.

2-(N-(4-Methoxyphenyl)formamido)ethyl formate (12b):^{15a} $R_f = 0.25$ (Petroleum ether:EtOAc, 2:1); 13.4 mg, 20% yield; light yellow liquid; ¹H NMR (600 MHz, Chloroform-*d*): δ 8.30 (s, 1H), 7.99 (s, 1H), 7.13 (d, J = 8.4 Hz, 2H), 6.93 (d, J = 8.4 Hz, 2H), 4.32 (t, J = 5.6 Hz, 2H), 4.04 (t, J = 5.6 Hz, 2H), 3.83 (s, 3H); ¹³C NMR (151 MHz, Chloroform-*d*): δ 162.8, 160.6, 158.9, 133.4, 126.7, 114.9, 60.6, 55.6, 44.5 60.6, 55.6, 44.5.

4-(N-(2-(Formyloxy)ethyl)formamido)benzoic acid (13b):^{15a} $R_f = 0.25$ (Petroleum ether:EtOAc:CH₃COOH = 50:50:1); 38.4 mg, 54% yield; white solid; m. p.: 122–123 °C; ¹H NMR (600 MHz, DMSO-*d*₆): δ 12.96 (s, 1H), 8.62 (s, 1H), 8.13 (s, 1H), 7.97 (d, *J* = 8.5 Hz, 2H), 7.48 (d, *J* = 8.7 Hz, 2H), 4.23 (t, *J* = 5.5 Hz, 2H), 4.12 (t, *J* = 5.5 Hz, 2H); ¹³C NMR (151 MHz, DMSO-*d*₆): δ 167.1, 163.0, 162.2, 145.0, 131.2, 128.6, 122.6, 60.6, 43.0.

2-(*N*-(**3,5-Dichlorophenyl**)formamido)ethyl formate (**14b**):^{15a} $R_f = 0.25$ (Petroleum ether:EtOAc = 5:1); 46.4 mg, 59% yield; light yellow liquid; ¹H NMR (600 MHz, Chloroform-*d*): δ 8.42 (s, 1H), 8.00 (s, 1H), 7.33–7.31 (m, 1H), 7.14 (s, 2H), 4.36 (t, *J* = 5.5 Hz, 2H), 4.07 (t, *J* = 5.5 Hz, 2H); ¹³C NMR (151 MHz, Chloroform-*d*): δ 161.8, 160.4, 142.8, 136.1, 127.3, 122.4, 60.5, 44.4.

N-(3,5-Dichlorophenyl)-*N*-(2-hydroxyethyl)formamide (14c): $R_f = 0.25$ (Petroleum ether: EtOAc = 2:1); 9.1 mg, (14c): $K_f = 0.23$ (refrom the energy of the contract of the

2-(N-(3,5-Dimethylphenyl)formamido)ethyl formate (**15b**):^{15a} $R_f = 0.25$ (Petroleum ether:EtOAc, 5:1); 39.2 mg, 59% yield; light yellow liquid; ¹H NMR (600 MHz, Chloroform-d): δ 8.36 (s, 1H), 7.99 (s, 1H), 6.96 (s, 1H), 6.80 (s, 2H), 4.32 (t, J = 5.7 Hz, 2H), 4.07 (t, J = 5.7 Hz, 2H), 2.34 (s, 6H); ¹³C NMR (151 MHz, Chloroform-d): δ 162.7, 160.6 140.5 130.7 120.0 122.3 (s) 4.41 2 132 160.6, 140.5, 139.7, 129.0, 122.3, 60.6, 44.1, 21.3.

2-(N-(3,4-Dimethylphenyl)formamido)ethyl formate (16b): 15a R_f = 0.25 (Petroleum ether: EtOAc = 3:1); 35.3 mg, (10): 12 K_f = 0.25 (redoledin ener.ElOAC = 5.1), 53.5 Hig, 53% yield; light yellow liquid; ¹H NMR (600 MHz, Chloroform-*d*): δ 8.34 (s, 1H), 7.98 (s, 1H), 7.16 (d, *J* = 8.0 Hz, 1H), 6.96–6.92 (m, 2H), 4.31 (t, *J* = 5.7 Hz, 2H), 4.06 (t, *J* = 5.7 Hz, 2H), 2.28 (m, 6H); ¹³C NMR (151 MHz, Chloroform-*d*): δ 162.7, 160.5, 138.3, 138.3, 136.0, 130.8, 125.9, 122.1, 60.6, 44.2, 19.8, 19.2.

2-(*N*-([1,1'-Biphenyl]-4-yl)formamido)ethyl formate **2-(N-([1,1'-Bipheny1]-4-y1)formamido)ethyl** formate (17b): $R_f = 0.25$ (Petroleum ether:EtOAc = 3:1); 51.5 mg, 64% yield; white solid; m. p.: 76–77 °C; ¹H NMR (600 MHz, Chloroform-*d*): δ 8.46 (s, 1H), 8.00 (s, 1H), 7.64 (d, J = 7.9 Hz, 2H), 7.59–7.57 (m, 2H), 7.46 (t, J = 7.7 Hz, 2H), 7.38 (t, J = 7.5 Hz, 1H), 7.28 (d, J = 8.2 Hz, 2H), 4.38 (t, J = 5.6 Hz, 2H); ¹³C NMR (151 MHz, Chloroform-*d*): δ 162.6, 160.6, 140.4, 139.8, 129.0, 128.5, 127.8, 127.0, 124.7, 60.7, 44.3; HRMS (ESI): m/z: calcd. for C₁₆H₁₅NO₃ (M+H)⁺: 270.1125; found: 270.1122.

2-(N-(Pyridin-2-yl)formamido)ethyl formate (18b):^{15a} R_f = 0.25 (Petroleum éther: EtOAc = 3.1); 33.2 mg, 57% yield; = 0.25 (Petroleum ether: EtOAc = 3:1); 33.2 mg, 57% yield; light yellow liquid; ¹H NMR (600 MHz, Chloroform-*d*): δ 9.12 (s, 1H), 8.43–8.42 (m, 1H), 7.99 (s, 1H), 7.76–7.74 (m, 1H), 7.17–7.14 (m, 2H), 4.42 (t, *J* = 5.8 Hz, 2H), 4.32 (t, *J* = 5.8 Hz, 2H); ¹³C NMR (151 MHz, Chloroform-*d*): δ 162.2, 160.7, 153.2, 148.8, 138.6, 120.6, 112.7, 61.0, 40.7.

2-(N-(Benzo[d]thiazol-2-yl)formamido)ethyl formate **2-(i7-(Benzold)(mazol-2-y))(ormalido)(etny)** formate (**19b):** $R_f = 0.25$ (Petroleum ether:EtOAc = 4:1); 33.4 mg, 45% yield; white solid; m. p.: 104–105 °C; ¹H NMR (600 MHz, Chloroform-*d*): δ 8.63 (s, 1H), 8.07 (s, 1H), 7.85–7.82 (m, 2H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.34 (t, *J* = 7.3 Hz, 1H), 4.62 (t, *J* = 4.9 Hz, 2H), 4.45 (t, *J* = 5.0 Hz, 2H); ¹³C NMR (151 MHz, Chloroform-*d*): δ 161.7, 160.3, 156.8, 147.8, 132.4, 126.3, 124.4, 121.7, 121.3, 61.0, 47.1; HRMS (ESI): m/z; celed, for C, $H = N_0 OS (M + N_0)^{+2}$, 273 0304; found: m/z: calcd. for $C_{11}H_{10}N_2O_3S$ (M+Na)⁺: 273.0304; found: 273.0300.

2-(N-(Dibenzo[b,d]furan-3-yl)formamido)ethyl formate **2-(N-(Dibenzo[b,d]furan-3-yl)formamido)ethyl formate** (**20b):** R_f = 0.25 (Petroleum ether:EtOAc = 3:1); 38.4 mg, 45% yield; yellow liquid; ¹H NMR (600 MHz, Chloroform *d*): δ 8.50 (s, 1H), 7.99–7.95 (m, 3H), 7.59 (d, *J* = 8.3 Hz, 1H), 7.51–7.48 (m, 1H), 7.44 (d, *J* = 1.9 Hz, 1H), 7.40–7.37 (m, 1H), 7.20–7.19 (m, 1H), 4.40 (t, *J* = 5.6 Hz, 2H); ¹³C NMR (151 MHz, Chloroform-*d*): δ 162.8, 160.5, 156.9, 156.5, 139.8, 127.7, 123.6, 123.3, 123.3, 121.5, 120.8, 119.5, 111.8, 108.3, 60.7, 44.8; HRMS (ESI): m/z: calcd. for C₁₆H₁₃NO₄ (M+H)⁺: 284.0917; found: 284.0913.

2-(N-(9-Phenyl-9H-carbazol-2-yl)formamido)ethyl

2-(N-(9-Phenyl-9H-carbazol-2-yl)formamido)ethyl formate (21b): $R_f = 0.25$ (Petroleum ether:EtOAc = 2:1); 66.3 mg, 62% yield; light yellow liquid; ¹H NMR (600 MHz, Chloroform-*d*): δ 8.45 (s, 1H), 8.14 (t, J = 7.9 Hz, 2H), 7.92 (s, 1H), 7.64 (t, J = 7.8 Hz, 2H), 7.55–7.50 (m, 3H), 7.45– 7.39 (m, 2H), 7.33–7.31 (m, 1H), 7.19 (d, J = 1.9 Hz, 1H), 7.11 (dd, J = 8.2, 1.9 Hz, 1H), 4.35 (t, J = 5.6 Hz, 2H), 4.13 (t, J = 5.6 Hz, 2H); ¹³C NMR (151 MHz, Chloroform-*d*): δ 163.0, 160.5, 141.7, 141.4, 138.7, 137.1, 130.2, 128.1, 127.1, 126.5, 122.6, 122.6, 121.4, 120.6, 120.4, 116.9, 110.0, 106.3, 60.8, 44.9; HRMS (ESI): m/z: calcd. for C₂₂H₁₈N₂O₃ (M+H)⁺: 359.1390; found: 359.1387.

2-(N-Phenylformamido)propyl formate (22b):^{15a} $R_f = 0.25$ (Petroleum ether:EtOAc = 3:1); 39.0 mg, 63% yield; light yellow liquid; ¹H NMR (600 MHz, Chloroform-*d*): δ 8.25 (s, 1H), 8.07 (s, 1H), 7.43 (t, *J* = 7.3 Hz, 2H), 7.41–7.38 (m, 1H), 7.20 (d, *J* = 7.6 Hz, 2H), 4.87–4.83 (m, 1H), 4.32–4.29 (m, 1H), 4.24–4.20 (m, 1H), 1.26 (d, *J* = 6.9 Hz, 3H); ¹³C NMR (151 MHz, Chloroform-*d*): δ 163.2, 160.6, 138.5, 129.7, 128.6, 128.5, 64.3, 49.8, 15.6.

Mixture of 1-(N-phenylformamido)propan-2-yl formate (23b)^{15a} and 2-(N-phenylformamido)ethyl acetate (23b)^{15a} $R_f = 0.25$ (Petroleum ether:EtOAc = 3:1); 50.0 mg, 81% yield; light yellow liquid; ¹H NMR (600 MHz, Chloroform-d): δ 8.39 (d, J = 7.1 Hz, 1.67H), 7.88 (s, 1H), $(23b)^{\overline{15}}$

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7.44–7.41 (m, 3.34H), 7.32–7.30 (m, 2H), 7.20 (t, J = 9.7 Hz, 3H), 5.27–5.24 (m, 1H), 4.26–4.24 (d, J = 5.8 Hz, 1.36H), 4.08–4.06 (m, 1.38H), 4.05–3.95 (m, 2H), 1.90 (s, 2H), 1.28 (d, J = 6.5 Hz, 3H); ¹³C NMR (151 MHz, Chloroform-*d*): δ 170.7, 162.9, 162.6, 160.4, 141.1, 129.9, 129.8, 127.3, 127.2, 124.5, 124.4, 68.4, 61.4, 49.2, 44.4, 17.9, 17.9.

2-(N-Phenylformamido)ethyl acetate (23b'):^{15a} $R_f = 0.25$ (Petroleum ether:EtOAc = 3:1); 20.1 mg, 32% yield; light yellow liquid; ¹H NMR (600 MHz, Chloroform-*d*): δ 8.40 (s, 1H), 7.42 (t, *J* = 7.9 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.21–7.20 (m, 2H), 4.25 (t, *J* = 5.6 Hz, 2H), 4.07 (t, *J* = 5.6 Hz, 2H), 1.90 (s, 3H); ¹³C NMR (151 MHz, Chloroform-*d*): δ 170.7, 162.5, 141.0, 129.7, 127.1, 124.5, 61.4, 44.3, 20.6.

1-(N-Phenylformamido)propan-2-yl acetate (24b):^{15a} R_f = 0.25 (Petroleum ether:EtOAc = 3:1); 55.0 mg, 83% yield; yellow liquid; ¹H NMR (600 MHz, Chloroform-*d*): δ 8.38 (s, 1H), 7.42 (t, *J* = 6.8 Hz, 2H), 7.31–7.28 (m, 1H), 7.18 (d, *J* = 7.8 Hz, 2H), 5.15–5.11 (m, 1H), 4.02–3.93 (m, 2H), 1.77 (s, 3H), 1.24–1.23 (m, 3H); ¹³C NMR (151 MHz, Chloroform-*d*): δ 170.1, 162.6, 141.2, 129.6, 126.8, 124.2, 68.7, 48.7, 20.7, 17.7.

1-(N-(3-Acetylphenyl)formamido)propan-2-yl acetate (25b): $R_f = 0.25$ (Petroleum ether:EtOAc = 3:1); 41.9 mg, 53% yield; light yellow liquid; ¹H NMR (600 MHz, Chloroform-*d*): δ 8.42 (s, 1H), 7.88 (d, *J* = 7.7 Hz, 1H), 7.83 (t, *J* = 2.0 Hz, 1H), 7.54 (t, *J* = 7.9 Hz, 1H), 7.41–7.39 (m, 1H), 5.16–5.11 (m, 1H), 4.06–3.95 (m, 2H), 2.64 (s, 3H), 1.81 (s, 3H), 1.25 (d, *J* = 6.4 Hz, 3H); ¹³C NMR (151 MHz, Chloroform-*d*): δ 196.9, 170.2, 162.4, 141.9, 138.6, 130.0, 128.4, 126.8, 123.4, 68.6, 49.0, 26.7, 20.9, 17.8; HRMS (ESI): m/z: calcd. for C₁₄H₁₇NO₄ (M+Na)⁺: 286.1050; found: 286.1048.

1-(N-(4-Acetylphenyl)formamido)propan-2-yl acetate **(26b):** $R_f = 0.25$ (Petroleum ether:EtOAc = 3:1); 41.7 mg, 53% yield; light yellow liquid; ¹H NMR (600 MHz, Chloroform-*d*): $\delta 8.51$ (s, 1H), 8.02 (d, J = 8.6 Hz, 2H), 7.29 (d, J = 10.1 Hz, 2H), 5.17-5.13 (m, 1H), 4.11-3.95 (m, 2H), 2.62 (s, 3H), 1.78 (s, 3H), 1.25 (d, J = 6.5 Hz, 3H); ¹³C NMR (151 MHz, Chloroform-*d*): $\delta 196.6$, 170.2, 162.2, 145.3, 135.1, 130.0, 122.8, 68.6, 48.5, 26.5, 20.9, 17.8; HRMS (ESI): m/z: calcd. for C₁₄H₁₇NO₄ (M+Na)⁺: 286.1050; found: 286.1053.

1-(N-(4-Chlorophenyl)formamido)propan-2-yl acetate (27b): $R_f = 0.25$ (Petroleum ether:EtOAc = 4:1); 41.2 mg, 54% yield; light yellow liquid; ¹H NMR (600 MHz, Chloroform-*d*): δ 8.35 (s, 1H), 7.39 (d, *J* = 8.1 Hz, 2H), 7.14 (d, *J* = 8.3 Hz, 2H), 5.13–5.10 (m, 1H), 3.99–3.90 (m, 2H), 1.81 (s, 3H), 1.23 (d, *J* = 6.4 Hz, 3H); ¹³C NMR (151 MHz, Chloroform-*d*): δ 170.2, 162.4, 139.9, 132.7, 129.8, 125.5, 68.7, 49.0, 20.9, 17.8; HRMS (ESI): m/z: calcd. for C₁₂H₁₄ClNO₃ (M+Na)⁺: 278.0554; found: 278.0556.

N-(4-Chlorophenyl)-*N*-(2-hydroxypropyl)formamide (27c): $R_f = 0.25$ (Petroleum ether:EtOAc = 2:1); 4.7 mg, 7% yield; light yellow liquid; ¹H NMR (600 MHz, Chloroform-d): δ 8.39 (s, 1H), 7.40–7.39 (m, 2H), 7.21–7.19 (m, 2H), 4.09–4.03 (m, 1H), 3.90–3.86 (m, 1H), 3.73–3.70 (m, 1H), 1.20 (d, *J* = 6.3 Hz, 3H); ¹³C NMR (151 MHz, Chloroform-d): δ 163.4, 140.2, 133.0, 129.9, 125.8, 66.5, 54.1, 21.3; HRMS (ESI): m/z: calcd. for C₁₀H₁₂ClNO₂ (M+H)⁺: 214.0629; found: 214.0626.

1-(N-(4-Cyanophenyl)formamido)propan-2-yl acetate (28b): $R_f = 0.25$ (Petroleum ether:EtOAc = 3:1); 38.1 mg, 52% yield; light yellow liquid; ¹H NMR (600 MHz, Chloroform-*d*): δ 8.50 (s, 1H), 7.74 (d, J = 8.6 Hz, 2H), 7.33 (d, J = 8.7 Hz, 2H), 5.18–5.12 (m, 1H), 4.11–4.08 (m, 1H), 3.96–3.92 (m, 1H), 1.79 (s, 3H), 1.25 (d, J = 6.5 Hz, 3H); ¹³C NMR (151 MHz, Chloroform-*d*): δ 170.1, 161.9, 145.3, 133.7, 123.3, 118.0, 110.1, 68.6, 48.6, 20.8, 17.8; HRMS (ESI): m/z: calcd. for $C_{13}H_{14}N_2O_3$ (M+Na)⁺: 269.0897; found: 269.0894.

1-(*N*-(3,5-Dimethylphenyl)formamido)propan-2-yl

acetate (29b): $R_f = 0.25$ (Petroleum ether:ÉtOAc = 5:1); 45.9 mg, 61% yield; yellow liquid; ¹H NMR (600 MHz, Chloroform-*d*): δ 8.34 (s, 1H), 6.93 (s, 1H), 6.78 (s, 2H), 5.13–5.10 (m, 1H), 3.99–3.88 (m, 2H), 2.33 (s, 6H), 1.81 (s, 3H), 1.23 (d, J = 6.4 Hz, 3H); ¹³C NMR (151 MHz, Chloroform-*d*): δ 170.3, 162.8, 141.1, 139.4, 128.6, 122.1, 68.8, 48.9, 21.2, 20.8, 17.8; HRMS (ESI): m/z: calcd. for C₁₄H₁₉NO₃ (M+Na)⁺: 272.1257; found: 272.1256.

4-(N-Phenylformamido)butanoic acid (1e): $R_f = 0.25$ (Petroleum ether:EtOAc:CH₃COOH = 100:100:1); 29.4 mg, 47% yield; light yellow liquid; ¹H NMR (600 MHz, Chloroform-*d*): δ 8.39 (s, 1H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.19 (d, *J* = 7.8 Hz, 2H), 3.89 (t, *J* = 7.3 Hz, 2H), 2.38 (t, *J* = 7.3 Hz, 2H), 1.91–1.86 (m, 2H); ¹³C NMR (151 MHz, Chloroform-*d*): δ 177.4, 162.9, 140.5, 129.8, 127.2, 124.2, 44.2, 31.1, 22.8; HRMS (ESI): m/z: calcd. for C₁₁H₁₃NO₃ (M+Na)⁺: 230.0788; found: 230.0782.

N-Butylaniline (2f):²⁹ $R_f = 0.25$ (Petroleum ether); 8.3 mg, 19% yield; light yellow liquid; ¹H NMR (600 MHz, Chloroform-*d*): δ 7.17 (t, J = 7.8 Hz, 2H), 6.71 (d, J = 7.5 Hz, 1H), 6.64 (d, J = 7.8 Hz, 2H), 3.11 (t, J = 7.3 Hz, 2H), 1.61 (p, J = 7.3 Hz, 2H), 1.46–1.40 (m, 2H), 0.95 (t, J = 7.0 Hz, 3H); ¹³C NMR (151 MHz, Chloroform-*d*): δ 148.1, 129.3, 117.6, 113.1, 44.1, 31.6, 20.3, 13.9.

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