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# Direct amidation of aniline derivatives with 1,1-dichloro-2nitroethene in water



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## Introduction

Amides are pervasive structural functionality for naturally occurring and artificial molecules, such as natural products, proteins, polymers, pharmaceuticals, and agrochemicals.<sup>1–4</sup> The development of efficient procedures for construction of amide bonds is a long-standing task for chemists.<sup>4,5</sup> The oldest and greenest formation of amides is developed by enzymes from carboxylic acids and amines.<sup>6</sup> Nowadays, the most conventional methods are coupling of amines with stoichiometrically activated carboxylic acids,<sup>7–9</sup> accounting for 93% of amidation in 128 drugs synthesis.<sup>6</sup> However, this method suffered from poor atom economy,<sup>10</sup> use of hazardous reagent<sup>11,12</sup> and complicated workup procedures.<sup>13,14</sup> Therefore, the greener procedures or novel catalysts for direct amidation have been developed in recent years.<sup>15,16</sup> These innovative strategies included, transamidation of amides under solvent-free conditions,<sup>17</sup> microwave irradiated direct amidation,<sup>18</sup> oxidative amidation of methylarenes,<sup>10</sup> metal-salts<sup>6,19</sup> or boron-reagents catalyzed amidation,<sup>6,20</sup> oxidative coupling of alcohols with amines,<sup>11,21</sup> mechanochemical synthesis of amides<sup>22</sup> and hydroamination of olefins.<sup>23</sup> Despite these progresses, direct amidation in water is still a challenging task due to its biocompatibility for the transformation of biologically relevant substrates.

1,1-Dichloro-2-nitroethene (DCNE) is a reactive intermediate used for insecticidal molecules construction. The strong electron-

## ABSTRACT

A green methodology was established for direct amidation of anilines using 1,1-dichloro-2-nitroethene. The new protocol provides convenient N-nitroacetylation for the anilines. This method was applicable to anilines include anthranilic acids, anthranilamides, phenylbenzohydrazides, diphenylamine, and 2-aminobenzenesulfonamide. The amidation process was accomplished in water and the products can be easily separated by filtration.

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withdrawing nitro group makes it reactive to amines, aryl alcohols or mercaptans (Fig. 1). Our recent explorations on reaction behaviors of DCNE revealed an efficient procedure for 1,3,4-oxadiazoles formation from hydrazides in water.<sup>24</sup> As an extension of DCNE research, we reported herein an efficient, catalyst-free and moisture insensitive method for amidation of aniline derivatives using DCNE.

## **Results and discussion**

Our previous success of high-yielding reactions of DCNE with hydrazides in water inspired us to screen the reaction conditions directly using water. Furthermore, the reaction can proceed smoothly without catalysts. Thus, the only variant for screening here was the temperature. DCNE and 2-amino-6-chlorobenzoic acid were selected as the model reaction. The reaction proceeded well at a wide range of temperatures with the lowest yields of 70% at 10 °C (Table 1). At 50 °C, the reaction reached the highest yield of 95%. The reaction rate was accelerated when elevating the temperature, but the yields slightly decreased. Therefore, the temperature of 50 °C was selected for further exploration. The success of using water as solvent can be partly explained by its high heat capacity to this exothermic reaction. Furthermore, water server as a reactant in the hydrolysis of the reaction intermediate.

The substrate scope evaluation commenced with different anthranilic acids (Scheme 1). Different sets of anthranilic acids having various substituent patterns underwent a smooth amide functionalization and delivered the desired products in excellent





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Figure 1. Reaction of DCNE with amines, aryl alcohols, mercaptans and hydrazides.

**Table 1**Screening of the temperature



<sup>a</sup> Product was isolated by filtration.

yields (up to 95%). Both electron-withdrawing (trifluoromethyl 3b, nitro 3e) and electron-donating (methoxyl 3d) groups were well tolerated. However, the reaction rate can be perturbed by the patterns of substituents, the substrate with electron-withdrawing trifluoromethyl (3b) and nitro (3e), long reaction time was needed for the completion of the amidation. Notably, the products precipitated from reaction mixture, which were easily separated through filtration. This conversion was applicable to anthranilamides (2i-2l) were also with good yields except substrate 2i, at milder conditions, probably due to the higher electrophilicity caused by the hyper-conjugation effect of methyl. Interestingly, the two main products of the reaction of 2i with DCNE were N-methyl-2-(2-nitroacetamido)benzamide 3i and N-(2-(3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)phenyl)-2-nitroacetamide 3I, which formed by further condensation of 2i and 3I with a 25% separated yield. However, the similar conversions were not observed on other anthranilamides.

We then extended the substrate scopes to other aniline derivatives. The phenylbenzohydrazides **2m** and **2n** were compatible with this protocol giving the corresponding amides in 74% and 57% yields, respectively. This transformation can also be subjected to the cyclic hydrazide **2o** with a yield of 45%. No reaction was observed on diarylhydrazide *N*-benzoylbenzohydrazide, which might be caused by the low basicity of nitrogen. This method was applicable to diphenylamine **2p** with moderate yields, but higher reaction temperature is needed to drive this conversion. The success of amidation of substrate 2p could be attributed to its steric hindrance for preventing the formation of 1:2 product as observed in aniline. Actually, trace amounts of amide product 2-nitro-N-phenylacetamide can be separated in the reaction of aniline with DCNE, although the major products were 2-nitro-N,N'diphenylethene-1,1-diamine. Reaction of 2-aminobenzenesulfonamide **2q** with DCNE afforded amide product **3q** with quite low yield. An array of unseparated side products formed for substrate **20–2q**, affecting the efficient nitroacetylation transformation. Reaction of 2-aminophenol with DCNE was also tested in water, but unfortunately, the cyclization occurred, which is consistent with the previous Letter (Fig. 1). The water solubility of 2i-2q is much lower than that of anthranilic acids, this low solubility feature resulted in the low transformation and impurity of the precipitates which needed further purification by silica gel column chromatography.

The scope observation suggested the high efficiency of this methodology to anthranilic acids with more than 90% yields. While other substrates gave moderate to low yields or complicated reactions this high compatibility to anthranilic acids prompted us to investigate the role of carboxyl group in the reaction. Several control experiments were run as depicted in Scheme 2. Splitting anthranilic acid to two starting materials benzoic acid and aniline was not feasible, but gave the similar reaction phenomenon with that of aniline. Changing the substituent position of carboxyl to meta- or para-one could not benefit the reaction with the production of more than four products which were not separated here, suggesting that the ortho-carboxyl was a preferable component for obtaining high yield of the desired products. Thus, we infer that the ortho-carboxyl group may play two roles here, that is, the formation of hydrogen bond with amino and the steric hinderance. Therefore, the ortho-substituent effects were further evaluated. A diminished reaction activity of *a*-nitroaniline implied that the nitro could stabilized the substrate, but still giving low fields of the product (less than 10%). Attempts of using dinitro-substituted amines 2,4-dinitroaniline and 2,6-dinitroaniline were met with no reaction even the reaction temperature was raised to reflux.

Treatment of ethyl 2-aminobenzoate was accomplished with the formation of an array of products. Substrate with high steric *tert*-butyl group can slow down the reaction rate but could not afford the high yield amide product, indicating that the steric effect



Scheme 1. Substrate scope investigation.

was not the determinant to the high yield. Excluding the electronic and steric effect, we proposed here that the *ortho*-carboxyl group may involve in the reaction. A plausible reaction pathway was proposed as shown in Scheme 3. For anthranilic acids, the reaction was initiated by the nucleophilic substitution of anthranilic acids to DCNE to give intermediate A, which underwent intramolecular cyclization affording intermediate B. Then the direct hydrolysis of B occurred giving intermediate C which tautomerized to the final product. While for other aniline substrates, direct hydrolysis of the carbon–chlorine bond occurred after the formation of anilineDCNE adducts D to get intermediate E, which tautomerized to final products.

#### Conclusion

In summary, an efficient direct amidation protocol for anilines was established using 1,1-dichloro-2-nitroethene. The reactions underwent in water and the products were easily separated by filtration. The presence of an *ortho*-carboxyl group is crucial for the high yields of the reactions. The electronic and steric effect of the









Scheme 3. Plausible reaction pathways.

substituent can also perturb the amidation reaction. This novel procedure provides an efficient and catalyst-free method for direct amidation of aniline derivatives using DCNE. The tolerance of the reaction to water creates the potential for the conversion of biomolecules.

## Experimental

Melting points (mp) were recorded on Büchi B540 apparatus (Büchi Labortechnik AG, Flawil, Switzerland) and are uncorrected. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on Bruker AM-400 (<sup>1</sup>H at 400 MHz, <sup>13</sup>C at 100 MHz, <sup>19</sup>F at 377 MHz) spectrometer with DMSO- $d_6$  as the solvent and TMS as the internal standard. Chemical shifts are reported in  $\delta$  (parts per million) values. High-resolution electron mass spectra (ESI-TOF) were performed on a Micromass LC-TOF spectrometer. High Resolution Mass Spectrometry (HRMS) were recorded under electron impact (70 eV) condition using a MicroMass GCT CA 055 instrument. Analytical thin-layer chromatography (TLC) was carried out on precoated plates (silica gel 60 F254) and spots were visualized with ultraviolet (UV) light. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, coupling constant (Hz) and integration.

## General procedure for the preparation of compounds

## General procedure for the preparation of 3a-3h

2-Aminobenzoic acid (2 mmol) and 1,1-dichloro-2-nitroethene (2.4 mmol) were added to 3 mL of water in a 10 mL round-bottom flask. Then stirred at 50 °C, after completion, the product precipitated from the reaction mixture and can be easily separated by filtration, then give the pure product.

#### General procedure for the preparation of 3i-3q

The substituted aniline compound (2 mmol) and 1,1-dichloro-2-nitroethene (2.4 mmol) were added to 3 mL of water in a 10 mL round-bottom flask and then stirred at the corresponding temperature, after completion. The mixture was purified by silica gel column chromatography (**3i–3l**, DCM/EA = 9:2; **3m–3q**, PE/EA = 3:1) to give the pure product.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.09. 048.

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