Synthesis of substituted urea or benzimidazolone using 1,1'-carbonyldiimidazole and substituted anilines

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Abstract   1,1'-carbonyldiimidazole (CDI) is a versatile reagent that can be used for synthesizing a variety of organic compounds containing carbonyl functional groups. The reactivity of CDI with two ortho-substituted anilines was tested and characterized with analytic techniques such as NMR, IR, and ESI-MS. A reaction of CDI with two equivalents of di-substituted aniline (N^1,N^1-diethylbenzene-1,2-diamine) formed a urea compound, 1,3-bis(2-(diethylamino)phenyl)urea (**1**). On the other hand, a reaction with one equivalent of mono-substituted aniline (tert-butyl (2-aminophenyl)carbamate) formed a substituted benzimidazolone, tert-butyl 2-oxo-2,3-dihydro-1H-benzo[d]imidazole-1-carboxylate (**2**). These results demonstrated that a singly substituted aniline prefers an intramolecular ring formation while an N,N-doubly-substituted aniline prefers a urea formation.

Keywords   1,1'-carbonyldiimidazole, CDI, urea, benzimidazolone

Introduction

1,1'-carbonyldiimidazole (CDI) is a safe and versatile reagent that can be used for preparing compounds with carbonyl functional groups such as carbonates, ureas, amides, urethanes, esters, etc.[1-8] Two imidazole substitution groups are replaced with amides or alkoxide by forming carbonyl-containing functional groups and imidazole. The formation of amides is especially important in the context of biological molecules with peptide bonds.

Due to their diverse chemical and biological properties, urea and its derivatives have been extensively used in chemical, pharmaceutical, and agrochemical industries.[9-11] Such fruitful urea compounds can be prepared by Curtis rearrangement, isocyanate treatment with amines, azide with amines, aldehyde with amines, CO_2 with amines, CDI with amines, etc. Preparation of urea using CDI is especially useful due to the formation of imidazole, which can be easily removed by the aqueous work-up processes.

Benzimidazolone is another important class of compound found in various organic and biological molecules.[12-15] Substituted benzimidazolones can also be prepared by various methods, including the intramolecular N-arylation of urea, carbonylation of 2-nitroaniline, carbonylation of o-phenyl-enediamine with CO_2, carbonylation of iminophosphorane with CO_2, and the reaction of CDI with mono-substituted anilines.

Here, we report the reactivity study of CDI with two substituted anilines. When CDI was treated with two equivalents of di-substituted aniline (N^1,N^1-

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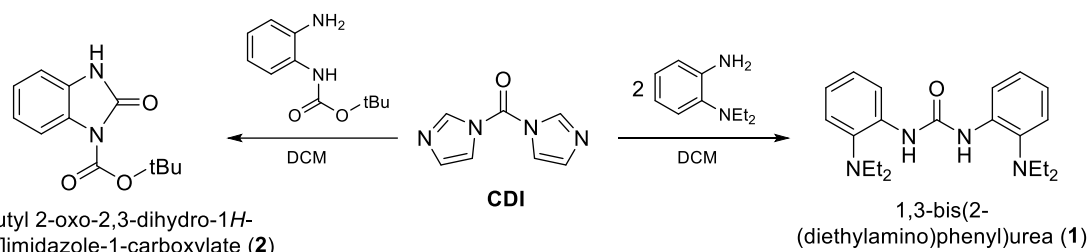
Scheme 1. Reactions of 1,1'-carbonyldiimidazole (CDI) with two equivalents of N^1,N^1-diethylbenzene-1,2-diamine (*right*) or one equivalent of tert-butyl (2-aminophenyl)carbamate (*left*).

diethylbenzene-1,2-diamine), a urea compound 1,3-bis(2-(diethylamino)phenyl)urea (**1**) was formed. A reaction with one equivalent of mono-substituted aniline (tert-butyl (2-aminophenyl)carbamate), however, formed a substituted benzimidazolone, tert-butyl 2-oxo-2,3-dihydro-1H-benzo[d]imidazole-1-carboxylate (**2**). The establishment of urea or benzimidazolone formation is useful for anion-sensing applications since some functional groups containing N-H moieties can be used as anion receptors.[16-17] Syntheses and characterizations will be discussed.

Experimental Methods

General considerations- All manipulations were carried out under an inert atmosphere using a nitrogen-filled glovebox or standard Schlenk techniques unless otherwise noted. All glassware was oven-dried prior to use. All solvents were degassed by sparging with ultra-high purity argon and dried via passage through columns of drying agents using a solvent purification system. N^1,N^1-diethylbenzene-1,2-diamine and tert-butyl (2-aminophenyl)carbamate were prepared following the literature.[18-19] All other chemicals were purchased from commercial vendors and used without further purifications.

Spectroscopic characterization and physical measurements- [^1]H NMR data were recorded on a Bruker DRX-300 instrument operating at 300 MHz. [^13]C NMR data were acquired on a DRX-500 or DPX-300 instrument operating at 125.8 and 75.4 MHz, respectively. Chemical shifts are reported in δ units in

ppm referenced to residual solvent peaks. The peak splitting patterns were assigned using the abbreviations s, d, t, q, and br for singlet, doublet, triplet, quartet, and broad, respectively. IR spectra were collected on a Thermo Scientific Nicolet iS-5 using an attenuated total reflection (ATR) accessory. The abbreviations vs, s, m, and w denote the very strong, strong, medium, and weak intensities of bands in the IR spectra, respectively. High-resolution MS data were obtained using a Waters instrument (Xevo G2-XS Tof) with an electrospray ionization (ESI) source and quadrupole time-of-flight (Q-TOF) analyzer system.

1,3-Bis(2-(diethylamino)phenyl)urea (1)- A mixture of 1,1'-carbonyldiimidazole (0.500 g, 3.08 mmol) and N^1,N^1-diethylbenzene-1,2-diamine (1.01 g, 6.17 mmol) in CH_2Cl_2 (20 mL) was heated at 50 °C in a sealed vial overnight. The resulting solution was allowed to cool down to room temperature and washed with DI water (30 mL) two times in the air. The organic layer was dried over Na_2SO_4, filtered, and evaporated to dryness under vacuum. Yield: 0.891 g (82%). [^1]H NMR (CDCl₃, 300 MHz): δ 8.18 (br s, NH, 2H), 8.14 (m, Ar-H, 2H), 7.19-7.11 (m, Ar-H, 4H), 7.00 (m, Ar-H, 2H), 2.93 (q, CH_2, 8H), 0.96 (t, CH_3, 12H). [^13]C{[^1]H} NMR (CDCl₃, 125.8 MHz): δ 152.73 (s, C=O), 139.05 (s), 137.04 (s), 125.76 (s), 122.88 (s), 122.46 (s), 118.67 (s), 49.27 (s), 13.07 (s). IR (ATR, cm⁻¹) 3256 m (N-H), 2964 m, 2926 w, 2840 w, 1652 s (C=O), 1584 s, 1507 vs, 1438 vs, 1385 w, 1368 m, 1328 w, 1292 m, 1241 m, 1220 w, 1189 s, 1171 s, 1147 m, 1014 m, 923 w, 895 w, 862 w, 808 w, 782 w, 740 vs, 627 w, 595 w, 489 m, 459 m, 415 w. HR-MS (ESI) *m/z*: calcd for $C_{21}H_{31}N_4O$
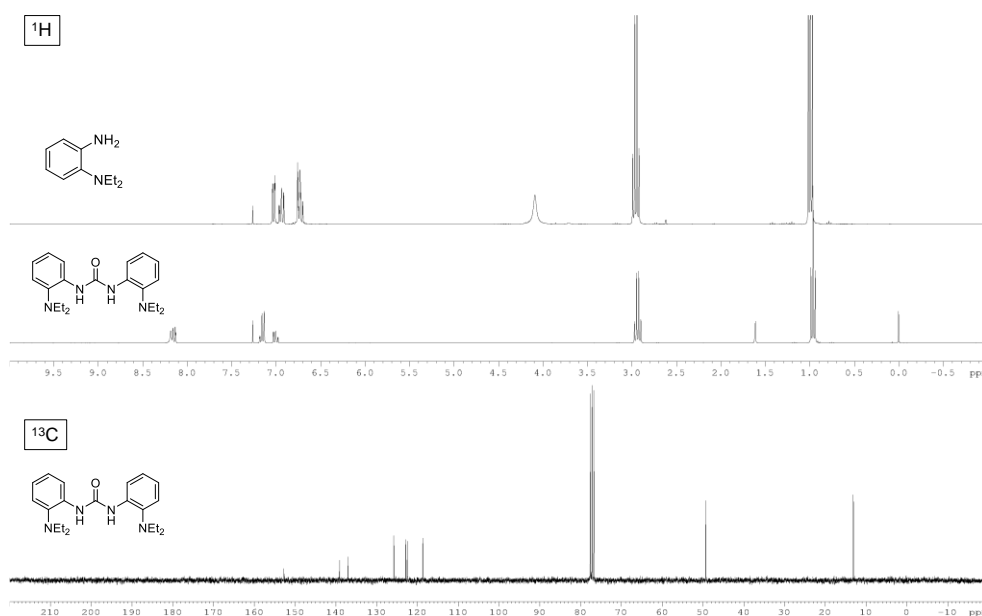
Figure 1. ^{1}H NMR spectra for N^1,N^1-diethylbenzene-1,2-diamine (*top*) and 1,3-bis(2-(diethylamino)phenyl)urea (**1**) (*middle*). ^{13}C NMR spectrum for **1** (*bottom*).
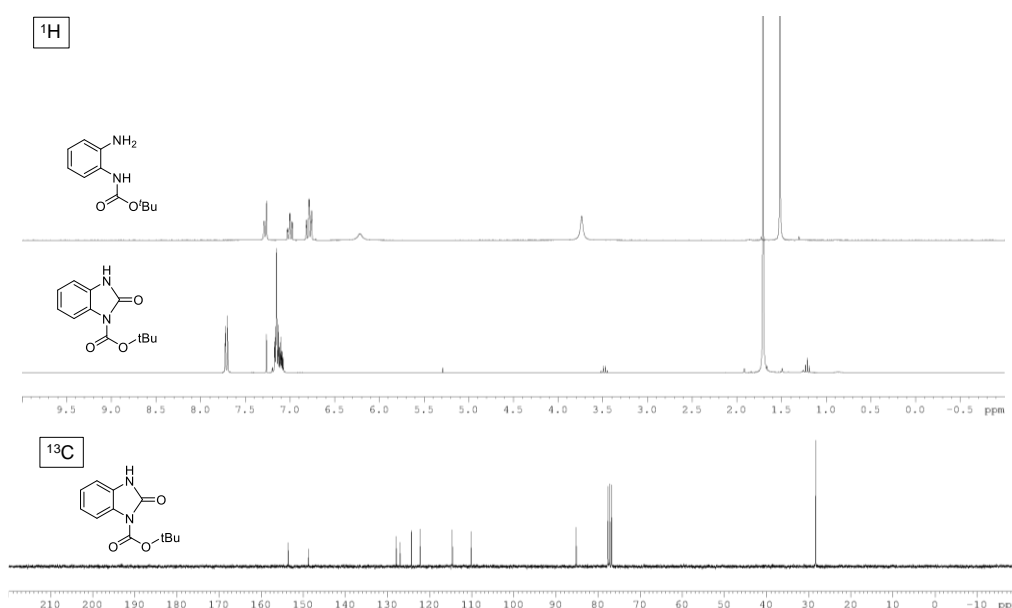
355.2498; found 355.2502.

Tert-butyl 2-oxo-2,3-dihydro-1H-benzo[d]imidazole-1-carboxylate (2)- A mixture of 1,1'-carbonyldiimidazole (0.100 g, 0.615 mmol) and tert-butyl (2-aminophenyl)carbamate (0.130 g, 0.625 mmol) in CH_2Cl_2 (10 mL) was heated at 50 °C in a sealed vial overnight. The resulting solution was allowed to cool down to room temperature and washed with DI water (30 mL) two times in the air. The organic layer was dried over Na_2SO_4, filtered, and evaporated to dryness under vacuum. Yield: 0.116 g (81%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.50 (br s, NH, 1H), 7.71 (m, Ar-H, 2H), 7.18-7.06 (m, Ar-H, 3H), 1.70 (s, CH_3, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75.4 MHz): δ 153.59 (s, C=O), 148.75 (s, C=O), 127.88 (s), 126.98 (s), 124.32 (s), 122.21 (s), 114.60 (s), 110.15 (s), 85.17 (s), 28.25 (s). IR (ATR, cm^{-1}) 3270 s (N-H), 2978 m, 1768 vs (C=O), 1622 w, 1607 w, 1479 s, 1453 w, 1394 m, 1371 m, 1340 vs, 1298 s, 1282 m, 1252s, 1149 vs, 1115 vs, 1027 w, 995 w, 931 w, 864 w, 838 s, 773 s, 754 vs, 696 s, 672 s, 640 m, 617 s, 574 w, 514 m, 456 m, 433 m, 411 w.

Results and Discussion

Reaction of CDI with N^1,N^1-diethylbenzene-1,2-diamine– . Treatment of CDI with two equivalents of N^1,N^1-diethylbenzene-1,2-diamine in CH_2Cl_2 formed 1,3-bis(2-(diethylamino)phenyl)urea (**1**) as confirmed by ^{1}H and ^{13}C NMR spectroscopy (Figure 1). A broad ^{1}H NMR resonance at δ 4.09 ppm for N^1,N^1-diethylbenzene-1,2-diamine shifted to downfield at δ 8.18 ppm, comparable to the resonance associated with NH (urea) of diphenylurea observed at δ 8.63 ppm. A singlet at δ 152.73 ppm observed in the ^{13}C NMR spectrum is comparable to carbonyl for diphenyl urea at δ 152.96 ppm.

The formation of **1** was further supported by FT-IR spectroscopy and high-resolution mass spectrometry. The observed IR bands at 3256 and 1652 cm^{-1} correspond to the stretching vibrations of N-H and C=O, respectively. In addition, the *m/z* 355.2502 in the HR-MS spectrum was acquired from the [M+H]$^+$ ion. The synthesis of substituted urea was successful when CDI was treated with two equivalents of N, N-doubly-substituted aniline. The absence of NH in an ortho

Figure 2. ^{1}H NMR spectra for tert-butyl (2-aminophenyl)carbamate (*top*) and tert-butyl 2-oxo-2,3-dihydro-1H-benzo[d]imidazole-1-carboxylate (**2**) (*middle*). ^{13}C NMR spectrum for **2** (*bottom*).

position exclusively drove the reaction to the formation of substituted ureas. In addition, simple washing with DI water completely removed the formed imidazole, which again demonstrates the usefulness of CDI in preparing urea compounds.

Reaction of CDI with tert-butyl (2-aminophenyl)carbamate – A CDI reaction with tert-butyl (2-aminophenyl)carbamate was also investigated using NMR spectroscopy (Figure 2). Broad resonances at δ 3.73 and 6.21 ppm for (2-aminophenyl)carbamate disappeared in the ^{1}H NMR spectrum, while a new broad singlet at δ 10.50 ppm appeared. Two singlets at δ 153.59 and 148.75 ppm in the ^{13}C NMR spectrum correspond to carbonyl functional groups. Overall, NMR spectroscopy confirmed the formation of tert-butyl 2-oxo-2,3-dihydro-1H-benzo[d]imidazole-1-carboxylate (**2**).

The formation of **2** was further supported using FT-IR spectroscopy. Absorption bands at 3270 cm^{-1} and 1768 cm^{-1} match those for N-H and C=O, respectively.

The CDI reaction with a singly-N-substituted benzenediamine prefers a benzimidazolone formation to a urea compound. The presence of an amine proton in an ortho position makes it possible to form a 5-membered-ring by an intramolecular carbonyl substitution reactions rather than the formation of urea by intermolecular carbonyl substitution reactions.

Conclusion

In summary, we have attempted the reactions of CDI with singly- or N,N-doubly-substituted anilines. The reaction of CDI with two equivalents of N^1,N^1-diethylbenzene-1,2-diamine formed a urea compound **1** by the intermolecular carbonyl substitution with two equivalents of aniline. The reaction of CDI with one equivalent of (2-aminophenyl)carbamate, however, formed a substituted benzimidazolone **2** by an intramolecular carbonyl substitution reaction. Given CDI's utility in synthesizing various carbonyl compounds, this strategy can be used to design synthetic methods for carbonyl compound preparations.

Acknowledgments

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