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A Cu-Catalyzed, pH-Neutral, Aerobic, Room Temperature Construction of High Enantiopurity Peptidyl Ketones from Peptidic S-Acylthiosalicylamides

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Abstract

Described herein is a Cu-catalyzed transformation of peptidic thiol esters and boronic acids into peptidyl ketones that takes place at room temperature in DMF or in DMF/H₂O open to air and uses only catalytic quantities of a Cu carboxylate to mediate the reaction. This aerobic transformation occurs only at a thiol ester capable of coordinating to Cu through its S-appendage and is hampered neither by racemization of the reactants or products, nor by the presence of disulfides or of unprotected phenols, alcohols, or indoles.

Keywords

C-C coupling; Cross-coupling; Synthetic methods; Copper; Peptidomimetics; Protein modifications

In recent decades great strides have been made in uncovering novel methods for the metal-catalyzed construction of C—C and C—X bonds from organic halides/sulfonates/phosphonates[1–11] and through C—H functionalization.[12–24] The great majority of these metal-catalyzed couplings are now carried out using mild organic transfer agents such as boronic acids, organostannanes, and organosilanes. The synthetic power and breadth of impact of these modern methods for the efficient and selective generation of a variety of bond types in a vast array of target molecules is unquestioned. And, yet, significant unmet challenges remain for the synthetic scientist to address. One holy grail is the highly chemoselective, non-enzymatic formation of a C—C or C—X bond at a specific site on a functionally complex biomolecule under biologically relevant conditions (i.e., minimal or no protecting groups, ambient temperatures, neutral pH reaction conditions, aerobic or anaerobic conditions, compatibility with protic solvents).[25–42]

New discoveries that can address this challenge will prove of significant value, both for the discovery and development of new therapeutics, and as diagnostic tools in chemical biology. We describe herein one contribution toward that goal: a Cu-catalyzed transformation of peptidyl thiol esters and boronic acids into peptidyl ketones,[43–60] which are important in the development of molecular therapeutics.[44,61–72] This new reaction takes place at room temperature in DMF or in DMF/H₂O open to air and uses only catalytic quantities of a Cu carboxylate to mediate the reaction. This aerobic transformation possesses high chemoselectivity occurring only at a thiol ester capable of coordinating to Cu through its *S*-appendage and is hampered neither by racemization of the reactants or products, nor by the presence of disulfides or of unprotected phenols, alcohols, or indoles. This chemistry is based upon a recently disclosed "second generation desulfitative coupling of thiol esters and boronic acids that takes place through a mechanistically novel *Cu-catalyzed*, aerobic desulfitative process.[73,74]

In probing the value of Cu-catalyzed, aerobic, desulfitative coupling for the construction of peptidyl ketones, a control experiment using tryptophan-derived thiol esters validated the importance of the nature of the thiol ester *S*-pendant on the substrate reactivity (Scheme 1): at 50 °C in DMF with 5 mol % Cu^I 3-methylsalicylate (CuMeSal) the reaction occurred only with the tryptophan derived thiophenyl ester bearing an *ortho* CONH*t*-Bu group and not with the simple thiophenyl ester.

This result clearly confirmed that a coordinating moiety on the pendant group of the thiol ester is a requisite condition for this Cu-catalyzed, aerobic reaction. As described in the initial manuscript disclosing the "second generation" desulfitative coupling,[73] the reaction is rendered catalytic in Cu under aerobic conditions through "scavenging" of the thiolate residue with a second sacrificial equivalent of the boronic acid. A Cu-centered transmetalation/reductive elimination sequence generates a thioether thus removing thiolate from the reaction system and regenerating Cu^I for subsequent reaction with O₂ and continuation of the catalytic cycle.

A brief study of the influence of the nature of the *ortho*-positioned amide group on the observed reaction rate and yield of peptidyl ketone formation was undertaken. Room temperature reaction conditions were used for this study, which benefited from an increase in the CuMeSal loading to 20 mol %. Four tryptophan derived thiol esters bearing different thiosalicylamide pendants NHMe, NH*i*-Pr, NH*t*-Bu, *N*-morpholino) were treated with 2.5 equiv of 2,4-difluorophenylboronic acid in the presence of 20 mol % CuMeSal in DMF at room temperature open to air (Figure 1). Missing from the series of thiosalicylamide pendants tested is the parent, –SC₆H₄CONH₂, whose handling and transformation proved unexpectedly problematic.

Among the four thiosalicylamides tested, the initial reaction rates inversely followed the steric encumbrance about the amide. The *N*-morpholino 3° amide-derived thiol ester gave the slowest initial reaction rate followed by –NH*t*Bu, –NH*i*Pr, and then –NHMe. The observed initial rates are consistent with a reaction that proceeds through a higher oxidation state Cu^{II/III} intermediate that templates the *S*-acylthiosalicylamide and the boronic acid for proximal orientation of the reactants and enhanced electrophilicity of the thiol ester (Scheme 2).[73] Diminished non-bonded steric effects make the less hindered amides better ligands for Cu, increasing the concentration of the Cu-templated species, and accordingly providing faster rates of reaction.

The different efficiencies of the four reactions are not fully understood at this time. The reactions of both the NH*i*-Pr and NH*t*-Bu amide substrates show excellent mass balances by HPLC analysis with all materials quantitatively accounted for in products and unreacted starting material. In contrast, no residual starting materials are apparent in the reaction of the NHMe amide, although the product yield maximizes at 71%. The *N*-morpholinyl amide

reaction does show some residual starting material by HPLC, even though the reaction stops after a low conversion to peptidyl ketone. Therefore, the best performing substrate was the somewhat hindered *NH*-Pr amide that reacted at a slower initial rate compared to the *NHMe* amide, but produced an excellent yield of the peptidyl ketone product within 90 minutes.

Examples of this room temperature, Cu-catalyzed, aerobic cross-coupling for the construction of peptidyl ketones are itemized in Table 1. A wide range of aryl (electron-rich, electron-deficient), heteroaryl (furyl, thienyl, benzothienyl, pyridinyl) and alkenyl boronic acids coupled efficiently with amino acid and a dipeptide derived thiol esters. Furthermore, sterically bulky boronic acids like 2-tolyl boronic acid and 2-*N*-Boc-pyrrolyl boronic acids gave peptidyl ketones in satisfactory yields. *n*-Butyl boronic acid, the only aliphatic boronic acid examined, did not produce a peptidyl ketone upon reaction with *N*-Cbz-*L*-Trp-*S*-C₆H₄(*o*-CONH*i*-Pr). In addition to the range of boronic acids that were useful, this reaction also tolerated thiol esters bearing metal binding and oxidation sensitive functional groups such as thioether (methionine), disulfide (cystine), unprotected indole (tryptophan), and unprotected phenol (tyrosine). From these examples, this reaction appears to be broadly useful in sensitive, functionally rich systems. This aerobic desulfitative cross coupling not only tolerates a broad spectrum of functional groups, but also inherits the stereo profile of the thiol ester substrates with high fidelity. For all the peptidyl ketones synthesized, neither racemization of the mono-peptidyl ketones nor epimerization of the dipeptidyl ketone was detected throughout the coupling reaction and the purification process.

This mild, Cu-catalyzed aerobic reaction is surprisingly tolerant various functional groups and of the presence of water. For example, using DMF/H₂O (2:1) as solvent, *N*-Boc-*L*-Phe-*S*-C₆H₄(*o*-CONH*i*-Pr) efficiently coupled with thiophene-2-boronic acid and produced the peptidyl ketone in 70% yield (accompanied by 73% of the mechanistically required thiol ether, 2-thienyl-*S*-C₆H₄(*o*-CONH*i*-Pr). The sensitivity of this reaction toward other functional groups was probed by the addition of stoichiometric additives to the Cu-catalyzed reaction of thiol ester *N*-Cbz-*L*-Trp-*S*-C₆H₄(*o*-CONH*i*-Pr) with 2,4-difluorophenylboronic acid.[75] The coupling reaction was unperturbed by the addition of stoichiometric quantities of a primary amine (benzylamine), a secondary amine (diisopropylamine) and a tertiary amine (triethylamine). The addition of a stoichiometric quantity of benzoic acid or of glucose did not hinder the formation the peptidyl ketone. However, the presence of salts like ammonium chloride and ammonium phosphate did inhibit the desired cross coupling reaction, possibly by perturbation of the catalytic process through anion binding with Cu.

In conclusion, Cu-catalyzed, aerobic, room temperature reaction conditions mediate the coupling of peptidic *S*-acylthiosalicylamides with boronic acids to provide good to excellent yields of high enantiopurity *N*-protected peptidyl ketones. Neither metal-binding nor oxidation sensitive peptide residues interfere with the reaction. Further investigations of this new reaction will be focused on the C—C bond functionalization of protein thiol esters[76–89] at both the C-terminus and side-chains,[90] on designing easily extractable thiosalicylamide residues to facilitate simple retrieval of the peptidic ketones, and on alternative Cu-catalyzed second generation desulfitative couplings that do not require two equivalents of the boronic acid.

Experimental Section

To a mixture of *N*-Cbz-*L*-Trp-*S*-C₆H₄(*o*-CONH*i*-Pr) (0.05 mmol, 26 mg, 1.0 equiv), 2,4-difluorophenylboronic acid (0.125 mmol, 20 mg, 2.5 equiv), Cu^I-3-methylsalicylate (0.01 mmol, 2 mg, 20 mol %) was added DMF (0.1 M based on the thiol ester). The reaction mixture was stirred under air at room temperature for 180 min after which time it was concentrated under vacuum to remove most of the DMF. The crude concentrate was then diluted with 10 volumes of ether. The ether solution was washed with water and the aqueous solution was

twice back extracted with same volume of ether. The combined organic layers were dried over MgSO_4 , filtered, and concentrated. The crude material was further purified by flash chromatography on silica gel with 20:1:5 CHCl_3 :EtOAc:hexanes to afford the peptidyl ketone as a yellow oil (21 mg, 97%) and the corresponding thio ether (16 mg, 99%). Peptidyl ketone data: TLC (R_f = 0.20, silica gel, CHCl_3 :EtOAc:hexanes = 20:1:5). HPLC Chiral OD-RH, λ = 254nm, Method: Flow: 1.0 mL/min; T = 30 °C; Gradient: 50% H_2O in CH_3CN during 10 min to 75% CH_3CN , during 12.5 min to 100% CH_3CN hold for 4.5 min, L-isomer t_R = 13.8 min, D-isomer t_R = 12.2 min, ee >99%. ^1H NMR (400 MHz, CDCl_3) δ 7.99 (s, 1H), 7.81 (dd, J = 14.8, 8.4 Hz, 1H), 7.35-7.27 (m, 7H), 7.14 (t, J = 7.6 Hz, 1H), 7.00 (t, J = 7.6 Hz, 1H), 6.93-6.80 (m, 3H), 5.67 (d, J = 7.6 Hz, 1H), 5.51 (dd, J = 13.2, 5.6 Hz, 1H), 5.11-5.04 (m, 2H), 3.44 (dd, J = 15.2, 5.6 Hz, 1H), 3.16 (dd, J = 14.8, 5.2 Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 195.5, 156.0, 136.6, 136.1, 133.5, 128.7, 128.3, 127.7, 123.0, 122.3, 119.8, 118.7, 112.8, 112.6, 111.3, 109.8, 105.3, 105.1, 104.8, 67.1, 60.0, 59.9, 27.8. IR (neat, cm^{-1}) 3405 (m), 1687 (s), 1610 (s), 1502 (m), 1235 (m), 972 (m), 741 (m). HRMS (FAB) Calcd for $\text{C}_{25}\text{H}_{21}\text{N}_2\text{O}_3\text{F}_2$ ($[\text{M}+\text{H}]^+$): 435.1514. Found: 435.1513. $[\alpha]_D^{20}$ +33.6 (c = 1.4, CHCl_3).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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90. Biological and chemical biological collaborative inquiries are welcome.

Figure 1. Influence of the Thiosalicylamide.^{a,b,c}

[a] a. $R^1 = H$, $R^2 = Me$; b. $R^1 = H$, $R^2 = i\text{-Pr}$; c. $R^1 = H$, $R^2 = t\text{-Bu}$; d. $R^1\text{--}R^2 = N\text{-morpholinyl}$.
 [b] For each thiol ester in Figure 1, two identical reactions were carried out, both containing decafluorobiphenyl as an internal standard. One reaction was used for HPLC analysis and the other to determine isolated yields of the peptidyl ketone at $T = 360$ min. No oxidative homocoupling of the boronic acid to the biphenyl was observed during the first 3 hours of the reaction.
 [c] In addition to the peptidyl ketone product, these reactions also generate (2,4- $C_6H_3F_2$) $S\text{-}C_6H_4(o\text{-CONH}i\text{-Pr})$, a mechanistically required side-product.

Scheme 1.

Control Experiments Demonstrating the S-Pendant Effect (Cbz = carbobenzyloxy; CuMeSal = Cu^I 3-methylsalicylate)

Scheme 2.
Putative Cu^{II/III}-Templated Intermediate

Table 1

Peptidyl Ketones via Aerobic Cu Catalysis^{a,b,c,d}

((Cbz = carbobenzyloxy))

[a] Isolated yields.

[b] Conditions: 1.0 equiv peptidyl thiol ester, 2.5 equiv boronic acid and 20 mol % Cu^I-3-methylsalicylate in DMF open to air at room temperature for 0.5 h – 24 h.

[c] ee was determined by reverse phase HPLC chiral OD, AD, AS and OJ column using racemic mixtures. In some cases the racemates were not resolved by HPLC and the ee's were not determined.

[d] In addition to the peptidyl ketone product, each reaction also generates a mechanistically required thioether side-product (R³S-C₆H₄(*o*-CONH*i*-Pr) formed from a sacrificial second equivalent of the boronic acid and the thiosalicylamide residue. The thioether side product is removed upon chromatographic purification of the peptidyl ketone. The Supporting Information provides full experimental details.