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Tetrahedron Letters
ELSEVIER
Tetrahedron Letters 48 (2007) 1867–1870

Unmasking of aminoanthroquinone moiety through a ring opening in the presence of copper salts and a subsequent cross-coupling/recyclization cascade

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Received 10 July 2006; revised 20 December 2006; accepted 21 December 2006
Available online 4 January 2007

Abstract—In the presence of copper(I) salts, 3-bromo- or 3-iodoisoxazoles undergo isoxazole ring opening to give keto amines that can undergo further one-pot cascade cross-coupling/recyclization transformation into an extended flat polyaromatic ring system that can provide an interesting new platform for the design of DNA intercalators. If necessary, the three-step reaction cascade can be interrupted at a desired intermediate step through a judicious choice of reaction temperature and catalyst.
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In this Lettter, we report a convenient three-step interruptible one-pot cascade transformation that we discovered during the preparation of hybrid molecules that combine the diverse biological activity of acetylene derivatives of azoles[1,2] with the ability of condensed 9,10-anthraquinones to intercalate the double-stranded DNA.[3,4]

Currently, the two mostly often utilized methods for the preparation of aryl- and hetarylacetylenes are those of Castro[5] and Sonogashira.[6] However, we found that the reaction of 3-iodoisoxazoles **1a,b** with copper phenyl acetylide in refluxing pyridine (the standard Castro conditions) leads to the formation of naphtho[2,3-*g*]indole-6,11-diones **4a,b** instead of the desired acetylenylisoxazoles.[7] The isoxazole formation can be envisioned as a three-step process that involves the cross-coupling of iodides **1a,b** with the copper phenyl acetylenide, opening of the isoxazole ring with concomitant reduction to anilines, and subsequent heterocyclization of 1-amino-2-phenylethynyl-9,10-anthraquinones **5a,b** into indoles **4a,b**. Remarkably, the overall process occurs under much milder conditions compared to that required for the thermal opening of the anthraisoxazole ring studied by us earlier.[8] a process which required 30–95 h at 152–177 °C depending on the substituents at the antraquinone core.

Silyl and alkyl substituted alkynes can also participate in the reactions described in Scheme 1. The structure of the ring opened cross-coupling products was unambiguously established through spectral and elemental analyses. The independently prepared (vide infra) aminoacetylenes **5a,b**[10] readily undergo cycloisomerization into the same condensed pyrroles **4a,b** in the presence of CuI at 150 °C in 57–97% yields. This finding contradicts the somewhat unexpected report[11] that the cyclization of vicinal aminoacetylenyl-9,10-anthraquinones to the respective naphthoindolodiones proceeds only in the presence of copper acetylide or copper powder, but not in the presence of copper halides (the typical catalysts for the similar cyclizations[5]). Thus, an interesting property of the ring opening/recyclization cascade is that it can be catalyzed by a variety of copper species including those required for both the Castro (copper acetylide) and Sonogashira (CuI) cross-coupling reactions.

Because the copper-catalyzed reductive isoxazole ring opening occurs at lower temperatures than the 5-*endo*-dig recyclization to indoles **4a,b**, the opening/cross-coupling/

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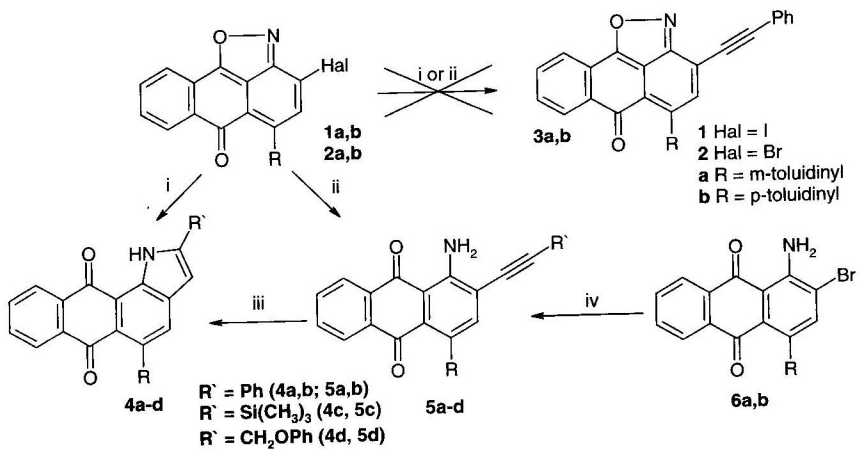
doi:10.1016/j.tetlet.2006.12.129



Scheme 1. Transformations of isoxazoles under Castro and Sonogashira conditions. Reagents and conditions: (i) CuC≡CR′, Py, 115 °C; (ii) HC≡CR′, C_6H_6, Et_3N, $Pd(PPh_3)_2Cl_2$, PPh_3, CuI, 45–50 °C; (iii) DMF, CuI, 155 °C; (iv) HC≡CPh, C_6H_6, Et_3N, $Pd(PPh_3)_2Cl_2$, PPh_3, CuI, 70 °C

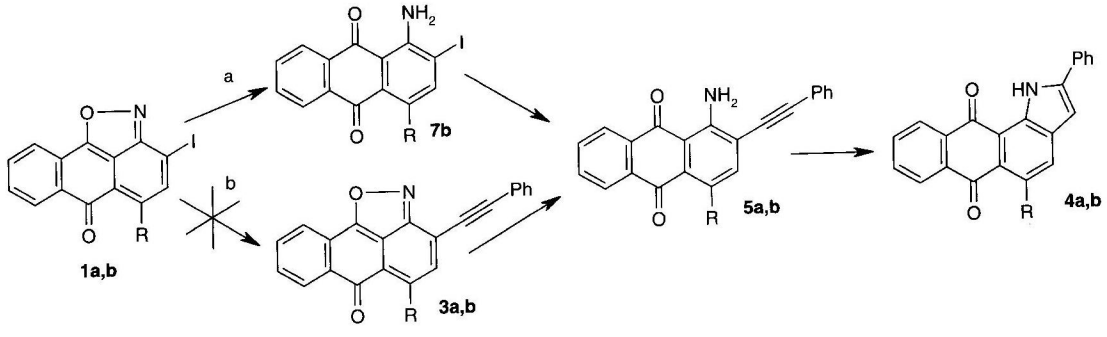
recyclization cascade can be stopped before the recyclization step to afford the respective acetylenic anilines in 62–65% yields when the cross-coupling reaction of iodides **1a,b** with a terminal acetylene is carried out under the milder Sonogashira conditions at 45–50 °C.[9] The possibility of interrupting this cascade process through the temperature control offers more flexibility in further synthetic applications of this process.

Several mechanistic questions arise when the overall reaction cascade process is considered. Is the ring opening purely thermal or does it require the presence of copper and/or palladium salts? At what stage does this process occur? In one plausible scenario (path a), the opening of iodoisoxazoles to iodoaminoanthraquinones occurs first and cross-coupling with the terminal acetylenes proceeds next. In an alternative path b, cross-coupling of iodoisoxazoles with terminal acetylenes proceeds in the first step and opening of the isoxazoles to 4-R-1-amino-2-(phenylethynyl)anthracene-9,10-diones **5a,b** happens at the next stage (Scheme 2).

Control experiments confirm the key role of copper salts and amines in the isoxazole ring opening.[12] For example, no changes were observed upon reflux of 1-iodoisoxazole with triphenylphosphine or phenyl acetylene in benzene for 2 h. Under the same conditions, the addition of Pd salts to the same mixture also does not lead to the ring opening. On the other hand, ring opening proceeds, albeit slowly, upon reflux in benzene or toluene in the presence of either Et_3N (8 h in refluxing benzene) or 120% of CuI (25% conversion after 13 h in refluxing toluene). In contrast, the formation of iodoamines **7a,b** is observed just after 5 min of reflux of **1a,b** with Et_3N in benzene when the Cu(I) iodide is present. The reaction was complete in 2 h and afforded ca. 70% of the product with the melting point and NMR data identical to the authentic sample.

Conveniently, the cross-coupling step with copper acetylide requires higher temperatures than the ring opening and, thus, even in the presence of acetylide, it is possible to stop the cascade transformation before the second (cross-coupling) step by controlling the temperature.

Thus, we established that under the mild conditions of the Sonogashira and Castro reactions, 3-bromo- or 3-iodoisoxazoles undergo isoxazole ring opening to give the respective 4-R-1-amino-2-(phenylethynyl)anthracene-9,10-diones. The diones undergo further one-pot cross-coupling/recyclization cascade transformation into an extended flat polyaromatic ring system that can provide an interesting new platform in the design of DNA intercalators and DNA cleaving agents.[13] If necessary, the reaction cascade can be stopped after the first step under the low temperature Castro conditions or after the second step under the low temperature Sonogashira conditions.



Scheme 2. Sequence of steps in the ring opening/cross-coupling/recyclization cascade.

The overall transformation is tightly choreographed—the isoxazole ring opening furnishes a keto amine moiety in which the carbonyl group activates the atom of iodine for the cross-coupling reaction (C–C bond formation), whereas the amino group provides the nitrogen atom for the C–N bond formation in the subsequent cyclization. Remarkably, in the Castro-based version of this process, all the three-steps in the reaction cascade are promoted through copper catalysis. The mechanism of the copper salt effect at the isoxazole ring opening and further synthetic explorations are under investigation.

Acknowledgments

This work was supported by a grant from the Ministry of Education and Science of Russian Federation (2006–2007) and grants 'Integration' of SB of Russian Academy of Sciences 132 and 154. Research at Florida State University was sponsored by the National Science Foundation (CHE-0316598) and Material Research and Technology (MARTECH) Center.

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5-(*m*-Toluidino)-2-phenyl-1*H*-naphtho[2,3*g*]indole-6,11-dione **4a** was obtained under the same conditions (8 h, from 695 mg of **1b**) (440 mg, 66%), mp 247–248 °C (benzene) IR, ν/cm^{-1} (KBr): 1621 (C=O); 3416 (NH). ^{1}H NMR, δ_H ($CDCl_3$-*d*): 2.38 (s, 3H, PhCH_3); 6.58 (s, 1H, 3-H); 6.96 (d, J = 7 Hz; 1H, 4′-H_{toluid}); 7.1–7.3 (m, 3H, 5′-, 6′-, 2′-H_{toluid}); 7.3–7.5 (m, 3H, 4-H, *m*-, *m*-H_{Ph}); 7.6–7.3 (m, 5H, 8-, 9-H, *o*-, *o*-, *p*-H_{Ph}); 8.1–8.4 (m, 2H, 7-, 10-H). HRMS, *m/z* (%): 428.0 [M]$^+$ (100.00), 427.1 (5.71), 413.0 (4.56), 212.0 (8.05), 411.0 (3.25), 213.9 (7.53), 206.4 (4.68), 177.9 (3.24), 28.0 (3.88). Found: *m/z* 428.15350 [M]$^+$. $C_{29}H_{20}N_2O_2$. Calcd: M = 428.15247.
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9. *Experimental procedure for the cross-coupling reaction with phenylacetylene*: A mixture of 5-(*p*-toluidino)-3-iodo-6*H*-anthra[1,9-*cd*]isoxazol-6-one **1b** (130 mg, 0.3 mmol), Et_3N (5 mL), $PdCl_2(PPh_3)_2$ (10 mg), PPh_3 (10 mg), CuI (10 mg), and phenylacetylene (46 mg, 0.45 mmol) in 10 mL of benzene was stirred under an argon stream at 45–50 °C for 9.5 h until iodide **1b** is consumed (TLC control: Silufol®). $CHCl_3$ (30 mL) and water (40 mL) were added. The organic layer was separated, the water layer was extracted with $CHCl_3$ (2 × 25 mL). The combined organic layers were washed with 25% aqueous NH_3 (2 × 15 mL), dried over sodium sulfate, and filtered through alumina (1 × 0.5 cm). The crude product was recrystallized from toluene, 4-(*p*-toluidino)-1-amino-2-phenylethynylanthracene-9,10-dione **5b** (80 mg, 65%), mp 207–208 °C (dioxane). IR, ν/cm^{-1} (KBr): 3458 (NH_2); 2203 (C≡C); 1612 (C=O). ^{1}H NMR, δ_H (DMSO-d_6): 2.35 (s, 3H, PhCH_3); 3.0 (br s, 1H, NH_2) 7.2–7.3 (m, 4H, *o*-, *o*-, *m*-, *m*-H_{toluid}); 7.4 (m, 3H, *m*-, *m*-, *p*-H_{Ph}); 7.62 (s, 3-H); 7.7 (m, 2H, *o*-, *o*-H_{Ph}); 7.9 (m, 2H, 6-, 7-H); 8.3 (m, 2H, 5-, 8-H); 11.93 (s, 1H, NH). HRMS, *m/z* (%): 428.1 [M]$^+$ (100.00), 427.2 (6.76), 412.2 (5.36), 214.1 (5.53), 73.1 (7.72), 43.2 (11.50), 41.1 (6.64), 32.0 (6.73), 29.0 (5.07), 28.0 (34.67). Found: *m/z* 428.15058 [M]$^+$. $C_{29}H_{20}N_2O_2$. Calcd: M = 428.15247. Compound **5b** was also prepared through an alternative route from aminobromide **6b** (Scheme 1, 3 h, 70 °C, 86%). 4-(*m*-Toluidino)-1-amino-2-phenylethynylanthracene-9,10-dione **5a** was obtained from isoxazole **2a** (3 h, 180 mg, 65%), mp 189–190 °C (toluene). IR, ν/cm^{-1} (KBr): 3449 (NH_2); 2203 (C≡C); 1620 (C=O). ^{1}H NMR, δ_H ($CDCl_3$-*d*): 2.37 (s, 3H, PhCH_3); 6.99 (d, J = 7 Hz, 1H, 4-H_{toluid}); 7.0–7.1 (m, 2H, 2-, 6-H_{toluid}); 7.3–7.4 (m, 4H, 5-H_{toluid}, *m*-, *m*-, *p*-H_{Ph}); 7.5–7.6 (m, 2H, *o*-, *o*-H_{Ph}); 7.7–7.8 (m, 3H, 3-, 6-, 7-H); 8.3–8.4 (m, 2H, 5-, 8-H). HRMS, *m/z* (%): 428.3 [M]$^+$ (100.00), 427.3 (14.32), 413.3 (11.69) 212.3 (22.56), 411.3 (11.76), 214.1 (15.14), 206.6 (13.67), 178.2 (10.43). Found: *m/z* 428.15651 [M]$^+$. $C_{29}H_{20}N_2O_2$. Calcd: M = 428.15247. Compound **5a** is prepared independently from aminobromide **6a** (Scheme 1, 23 h, 70 °C, 92%).
10. A mixture of 4-(*p*-toluidino)-1-amino-2-(phenylethynyl)anthracene-9,10-dione (430 mg, 1 mmol) and CuI (150 mg) in 10 mL of DMF was stirred under the stream of argon at 50 °C for 2 h until all **5b** is consumed (TLC control). $CHCl_3$ (20 mL) and water were added, the organic layer was separated, the water layer extracted with $CHCl_3$ (2 × 5 mL), and the combined organic layer was washed with 25% NH_{3aq} (3 × 35 mL), dried over sodium sulfate, and filtered off through alumina (1 × 0.5 cm). The crude product was purified by recrystallization from dioxane, 5-(*p*-toluidino)-2-phenyl-1*H*-naphtho[2,3-*g*]indole-6,11-dione **4b** (420 mg, 97.6%) mp 256–257 °C (benzene). 5-(*m*-Toluidino)-2-phenyl-1*H*-naphtho[2,3-*g*]-indole-6,11-dione **4a** was obtained under analogous conditions (750 mg, 58%), mp 247–248 °C (benzene).
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12. Opening of the isoxazole ring in the cross-coupling reaction with PhC≡CCu [copper(I) phenylacetylide]:

Iodide **1b** (130 mg, 0.3 mmol) and PhC≡CCu (50 mg, 0.36 mmol) in 5 mL pyridine were heated (3 h) at 70 °C under an argon atmosphere (TLC control: Silufol®). The reaction mixture was cooled, poured into chloroform, and washed with aqueous ammonium hydroxide. After chloroform solution was dried over sodium sulfate and filtered through alumina (height/diameter of the column: 1 × 0.5 cm), the solvent was eliminated under reduced pressure. The products were recrystallized (120 mg, 92%) mp 199–200 °C (benzene). IR, ν/cm^{-1} (KBr): 3412 (NH); 1620 (C=O). ^1H NMR, δ_H ($CDCl_3$-*d*): 2.36 (s, 3H, PhCH_3); 3,7 (s, br, 2H, NH_2); 7.0–7.23 (m, 4H, H_{toluid}); 7.7–7.8 (m, 2H, 6-, 7-H); 8.03 (s, 1H, 3-H); 8.2–8.3 (m, 2H, 5-, 8-H); 11.79 (s, 1H, NH). HRMS, *m/z* (%): 453.8 [M⁻] (100.00), 452.8 (2.73), 328.1 (2.82), 327.0 (10.13), 326.0 (2.96), 312.0 (7.51), 227.1 (2.76), 163.6 (2.74). Found: *m/z* 454.01761 $[M]^+$. $C_{29}H_{20}N_2O_2$. Calcd: M = 454.01798.

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