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Heterocycle–Heterocycle Strategies: (2-Nitrophenyl)isoxazole Precursors to 4-Aminoquinolines, 1*H*-Indoles, and Quinolin-4(1*H*)-ones

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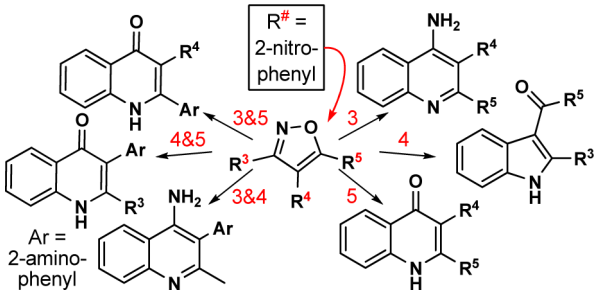
ABSTRACT



Reductive heterocycle–heterocycle (heterocycle → heterocycle; H–H) transformations that give 4-aminoquinolines, 3-acylindoles, and quinolin-4(1*H*)-ones from 2-nitrophenyl substituted isoxazoles are reported. When this methodology is applied to 3,5-, 4,5-, and 3,4-bis(2-nitrophenyl)isoxazoles, chemoselective heterocyclization gives quinolin-4(1*H*)-ones, and 4-aminoquinolines, exclusively.

In diversity oriented syntheses,[1] heterocycle–heterocycle (**H–H**) strategies, wherein a starting heterocycle is transformed into a new and architecturally different heterocycle, constitute a powerful means to address diversity in discovery chemistry.[2] We postulate that **H–H** strategies can be particularly useful in providing skeletal diversity and that this approach uniquely complements the more well established 'reagent-based' and 'substrate-based' approaches to skeletal diversification.[3] Indeed, we have recently exploited an **H–H** strategy in a variety of indazole → indazolone studies[4] and report an extension to isoxazole based systems.

From previous work,[5] substituted (3- and 4- nitrophenyl)-isoxazoles can be selectively reduced to their corresponding anilines with Zn/HOAc (0 °C, 5 min) and we set out to explore the possibility of reducing 2-nitrophenylisoxazoles to other useful heterocycles with Zn/HOAc. Analysis of the

(1) (a) Schreiber, S. L. *Science* **2000**, *287*, 1964. (b) Galloway, W. R. J. D.; Isidro-Llobet, A.; Spring, D. R. *Nat. Commun.* **2010** DOI: 10.1038/ncomms1081, 1. (c) Patil, N. T.; Shinde, V. S.; Sridhar, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 2251. (d) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46. (e) Tan, D. S. *Nat. Chem. Biol.* **2005**, *1*, 74. (f) Schreiber, S. L. *Nature* **2009**, *457*, 153. (g) Thomas, G. L.; Wyatt, E. E.; Spring, D. R. *Curr. Opin. Drug Discovery Dev.* **2006**, *9*, 700.

(2) (a) Guirado, A.; Andreu, R.; Martinez, B.; Bautista, D.; Arellano, C. R.; Jones, P. G. *Tetrahedron* **2006**, *62*, 6172. (b) Fahmy, A. F. M. *ARKIVOC* **2006**, *7*, 395. (c) Guirado, A.; Andreu, R.; Galvez, J. *Tetrahedron Lett.* **2003**, *44*, 3809. (d) Pace, A.; Pibiri, I.; Buscemi, S.; Vivona, N. *Heterocycles* **2004**, *63*, 2627. (e) Piccionello, A. P.; Guarcello, A.; Buscemi, S.; Vivona, N.; Pace, A. *J. Org. Chem.* **2010**, *75*, 8724.

(3) (a) Galloway, W. R. J. D.; Diáz-Gavilán, M.; Isidro-Llobet, A.; Spring, D. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 1194. (b) Morton, D.; Leach, S.; Cordier, C.; Warriner, S.; Nelson, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 104. (c) Spandl, R. J.; Bender, A.; Springer, D. R. *Org. Biol. Chem.* **2008**, *6*, 1149. (d) Kumagai, N.; Muncipinto, G.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 3635.

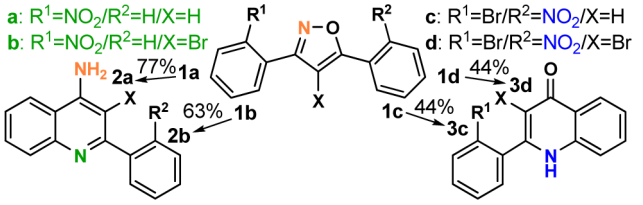
(4) (a) Conrad, W. E.; Rodriguez, K. X.; Nguyen, H. H.; Fettinger, J. C.; Haddadin, M. J.; Kurth, M. J. *Org. Lett.* **2012**, *14*, 3870. (b) Conrad, W. E.; Fukazawa, R.; Haddadin, M. J.; Kurth, M. J. *Org. Lett.* **2011**, *13*, 3138. (c) Donald, M. B.; Conrad, W. E.; Oakdale, J. S.; Butler, J. D.; Haddadin, M. J.; Kurth, M. J. *Org. Lett.* **2010**, *12*, 2524. (d) Oakdale, J. S.; Solano, D. M.; Fettinger, J. C.; Haddadin, M. J.; Kurth, M. J. *Org. Lett.* **2009**, *11*, 2760.

(5) (a) Coffman, K. C.; Hartley, T. P.; Dallas, J. L.; Kurth, M. J. *ACS Comb. Sci.* **2012**, *14*, 280. (b) Butler, J. D.; Coffman, K. C.; Ziebart, K. T.; Toney, M. D.; Kurth, M. J. *Chem.—Eur. J.* **2010**, *16*, 9002.

10.1021/ol400787y

literature revealed that others had reported related transformations. Specifically, Batra[6a] et al. reported that a palladium on carbon-mediated reduction of 3-(2-nitrophenyl)-isoxazole leads to substituted 4-aminoquinolines (10 examples)[6] and Yamanaka et al. reported that Raney nickel reduction of 4- or 5-(2-nitrophenyl)isoxazoles can deliver 3-acylindole[7] (2 examples) or quinolin-4(1*H*)-one[7b] (1 example) heterocycles, respectively.

Scheme 1. H−H Chemistry of 3- and 5-(2-Nitrophenyl)-isoxazoles



This backdrop, coupled with the **H−H** potential of this strategy, led us to explore this topic further, focusing initially on using M (= Zn or Fe) in HOAc to transform (2-nitrophenyl)isoxazoles into quinolines/indoles/quinolin-4(1*H*)-ones with subsequent studies exploring the outcomes of reducing bis(2-nitrophenyl)isoxazoles under these same conditions. We began by preparing (2-nitrophenyl)isoxazole **1a** (Scheme 1) and found that this substituted isoxazole did not reduce in Zn/HOAc at rt. Fortunately, we found that Fe powder in neat HOAc at 120 °C resulted in reductive heterocyclization to 4-aminoquinoline **2a** in 77% yield. To extend this methodology, isoxazole **1a** was cleanly converted to 4-bromoisoxazole **1b** (Br_2, CCl_4, 99% yield) and subsequent Fe/HOAc reduction delivered 3-bromo-4-aminoquinoline (**2b**). Attempts to combine this **1b** → **2b H−H** transformation with subsequent *o*-haloaniline-based coupling reactions failed. These reductive heterocyclizations of **1a** and **1b** proceed by the green aniline NH_2 attacking the isoxazole-derived carbonyl.

We next prepared isoxazole **1c** by reacting 2-bromo-*N*-hydroxybenzimidoyl chloride with 2-nitrophenylacetylene.[8] Fe/HOAc reduction of isoxazole **1c** gave 2-(2-bromophenyl)-4-quinolin-4(1*H*)-one **3c** in 44% yield. We found that Br_2 in CCl_4 was ineffective at C4 bromination of isoxazole **1c**; it was however readily brominated to **1d** using NBS (HOAc, cat. H_2SO_4). Fe/HOAc reduction of **1d** gave 3-bromo-2-phenyl-4-quinolin-4(1*H*)-one **3d** (44% yield).

(6) (a) Singh, V.; Yadav, G. P.; Maulik, P. R.; Batra, S. *Synthesis* **2006**, *12*, 1995. (b) Casnati, G.; Quilico, A.; Ricca, A.; Finzi, P. V. *Tetrahedron Lett.* **1966**, *7*, 233. (c) Thomson, I.; Torssell, K. B. G. *Acta Chem. Scand., Ser. B* **1988**, *42*, 309. (d) Jensen, S.; Torssell, K. B. G. *Act. Chem. Scand.* **1995**, *49*, 53.

(7) (a) Uchiyama, D.; Yabe, M.; Kameyama, H.; Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Heterocycles* **1996**, *43*, 1301. (b) Sakamoto, T.; Kondo, Y.; Uchiyama, D.; Yamanaka, H. *Tetrahedron* **1991**, *47*, 5111.

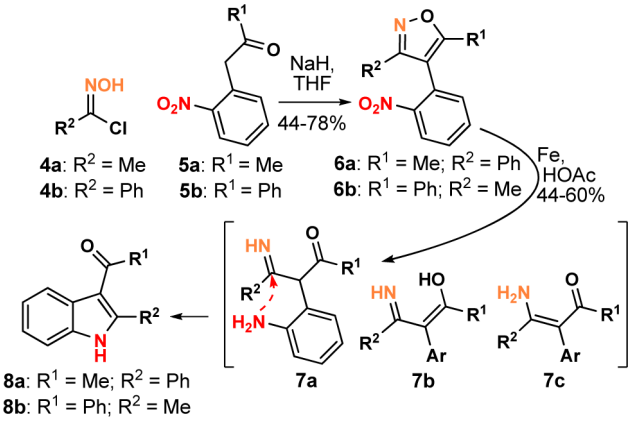
(8) (a) Guggenheim, K. G.; Butler, J. D.; Painter, P. P.; Lorsbach, B. A.; Tantillo, D. J.; Kurth, M. J. *J. Org. Chem.* **2011**, *76*, 5803. (b) Meng, L.; Lorsbach, B. A.; Sparks, T. C.; Fettinger, J. C.; Kurth, M. J. *J. Comb. Chem.* **2010**, *12*, 129.

As with **2b**, all attempts at metal-mediated[9] reactions on **3d** [→ 5*H*-indolo[3,2-*b*]quinolin-11(10*H*)-one] failed. The reductive heterocyclizations of **1c** and **1d** proceed by the blue aniline NH_2 attacking the isoxazole-derived imine carbon.

With these calibrating results in hand, wherein both the carbonyl and imine carbons can serve as the reactive electrophile, our next objective was to evaluate whether presumed intermediate **7** (Scheme 2) would undergo chemoselective heterocyclization of the red aniline NH_2 onto the imine or onto the carbonyl carbon. Each heterocyclization of **6** would deliver a different 3-acylindole when $R^1 \neq R^2$. To address this competition question, both isomers of **6** (**a** and **b**) were prepared by the base-mediated condensation of the appropriate chlorooxime **4** with the appropriate 1-(2-nitrophenyl)alkan-2-one **5** (→ **6a**; → **6b**).

In the event, reduction of **6a** under Fe/HOAc conditions gave only indole **8a** in 46% yield. Likewise, reduction of **6b** gave only indole **8b** in 60% yield (see X-ray in Supporting Information (SI)).[10] In both cases, the aniline NH_2 cyclized

Scheme 2. H−H Chemistry of 4-(2-Nitrophenyl)isoxazole



with complete chemoselectivity onto the imine carbon of **7**.[11] Although intermediate **7** has several possible tautomeric forms that are all likely accessible under the reaction conditions[12] and may display different modes of reactivity, the observed chemoselectivity is complete. Although we are not certain which tautomeric form (or protonated form thereof) of **7** preferentially reacts in the systems described herein, we formulate our discussion around the *β*-iminocarbonyl **7a**.

To test the limits of imine vs carbonyl chemoselectivity, **6c** was prepared (Scheme 3). Our reasoning was that a

(9) For a review of Buchwald chemistry, see: Fischer, C.; Koenig, B. *Beilstein J. Org. Chem.* **2011**, *7*, 59.

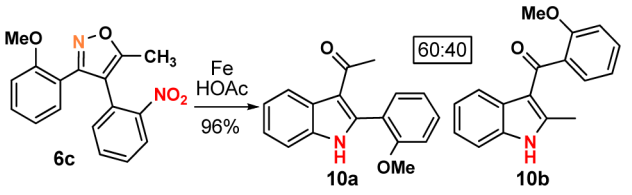
(10) CCDC 926644 (**8b**), 926905 (**10a**), and 926645 (**10b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(11) See Supporting Information for explanation of chemoselectivity.

(12) Tautomer energies of **7a**, **7b**, and **7c** (R^3 = Ph, R^4 = H, R^5 = Ph) were computed (B3LYP/6-31+G(d,p); see SI for complete details). It was determined that **7c** had the lowest overall energy, while **7a** and **7b** were 10.1 and 5.2 kcal/mol higher, respectively.

2-methoxyphenyl moiety (R^2 in **7**; Scheme 2) would donate electron density into the imine of **7** and reduce its electrophilicity. Treating **6c** with Fe/HOAc at 120 °C resulted in the formation of two indole products, **10a** and **10b** in a combined yield of 96% and in a 60:40 ratio, respectively. Thus, even in this "reactivity-skewed" case, the aniline NH_2 prefers to attack the imine (**9a** → **10a**), in contrast to Yamanaka's one asymmetrical example.[7a] The structures of **10a** and **10b** were established by X-ray crystallography (see SI).[10]

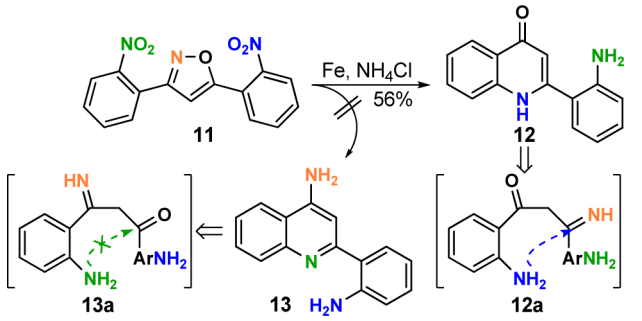
Scheme 3. H−H Chemistry of 4-(2-Nitrophenyl)isoxazole



With these Fe/HOAc-mediated (2-nitrophenyl)isoxazole → 4-aminoquinoline/indole/quinolin-4(1*H*)-one **H−H** results in hand, we next explored the reductive heterocyclization chemistry of 3,5-, 3,4-, and 4,5-bis(2-nitrophenyl)-isoxazoles as it appeared these systems would confront new, as yet unexplored chemoselectivity questions. For example, reductive heterocyclization of 3,5-bis-(2-nitrophenyl)-isoxazole **11** (Scheme 4) could produce quinolin-4(1*H*)-one (⇒ heterocyclization to **12** involving the imine via **12a**) and/or 4-aminoquinoline (⇒ heterocyclization to **13** involving the carbonyl via **13a**) products. To probe this question, **11** was synthesized.

Reductive heterocyclization of **11** with Fe/HOAc gave quinolin-4(1*H*)-one **12** (22% isolated + several unidentified spots in the crude TLC); we suspected that in situ formation of acetic anhydride and subsequent *N*-acylation(s) of the reaction products complicated this reaction mixture.[13] It was found that changing the acid source from HOAc to aq. NH_4Cl increased the yield of **12** to 56%. Thus, **11**, upon reduction, leads to chemoselective attack by the blue aniline NH_2 onto the imine carbon (**12a** → **12**) to the complete exclusion of the green aniline NH_2 onto the carbonyl carbon (**13a** → **13**). Importantly, no 4-aminoquinoline **13** was detected in either reaction.[14] Again, understanding the heterocyclization reactivity of bis(2-nitrophenyl)isoxazole derived intermediates is complicated by the viability of various β-iminocarbonyl tautomers, their numerous conformations and configurations, multiple possible hydrogen bonding arrays, the effects of different conjugation pathways on the acidity/basicity (and, potentially, iron-binding ability) of key functional groups, and different tether lengths between potential nucleophiles and electrophiles (6-exo-trig vs 5-exo-trig).[15] Despite these complications, the **H−H** reductive heterocyclizations depicted in Schemes 2 and 4 each proceed to give only one new heterocyclic product.

Scheme 4. H−H Chemistry of 3,5-Bis(2-nitrophenyl)isoxazole



The complete imine vs carbonyl chemoselectivity observed for **11** suggested that 3,4-bis(2-nitrophenyl)-isoxazole **14** (Scheme 5) should produce 3-acyl-1*H*-indole **17** (and, perhaps, its condensation analogue **18**). To test this hypothesis, 1-(2-nitrophenyl)-propan-2-one was condensed with *N*-hydroxy-2-nitrobenzimidoyl chloride (NaH in dry THF). Reductive heterocyclization of **14** with Fe/HOAc gave none of the anticipated imine-derived indole **17**; rather, 4-aminoquinoline **15** and its acylated analogue **16** (69% combined yield; 0.2:1 ratio, respectively) were produced.

Obtaining **16** supports the suspected in situ formation of acetic anhydride under these conditions.[13] Since neither indole **17** or **18** was obtained, we believe that this heterocyclization is prevented because the imine in **17a** (→ **17**) suffers deactivation by conjugation with the green aniline NH_2 (similar to **6c**; Scheme 3). Accepting that as an explanation for no formation of **17**, why was 4-aminoquinoline **15** formed to the complete exclusion of indole **19**? We hypothesize that the red aniline NH_2 (derived from the red nitro moiety) is the most basic site in the bis-reduction intermediate derived from **14**: this nitrogen's lone pair is not delocalized into the β-iminocarbonyl system whereas the green aniline NH_2 would be. Consequently, in acetic acid at 120 °C, the red aniline is protonated (see **15a** in Scheme 5) and not available for the required nucleophilic attack. Indeed, this factor may also explain the lack of formation of **17**.

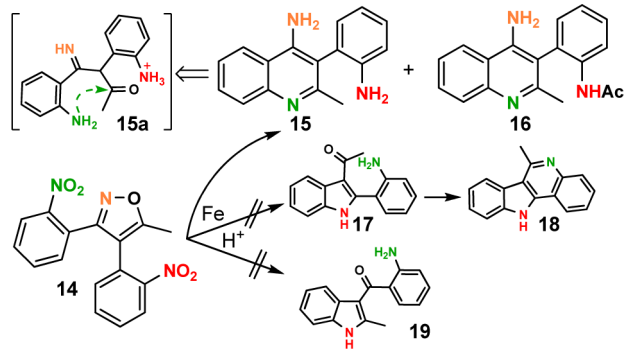
These insights with **14** led us to predict that reductive heterocyclization of the final system in this series, i.e., 4,5-bis-(2-nitrophenyl)isoxazole **20** (Scheme 6), should produce quinolin-4(1*H*)-one **21a** (⇒ reductive heterocyclization of **20** to **21a** would involve the imine carbon and the blue conjugated aniline NH_2) via intermediate **20a**. To test

(13) For related studies, see: (a) Yamada, Y.; Segawa, M.; Sato, F.; Kojima, T.; Sato, S. *J. Mol. Catal. A: Chem.* **2011**, *346*, 79. (b) Karimi, E.; Teixeira, I. F.; Ribeiro, L. P.; Gomez, A.; Lago, R. M.; Penner, G.; Kycia, S. W.; Schlaf, M. *Catal. Today* **2012**, *190*, 73. (c) Squibb, E. R. *J. Am. Chem. Soc.* **1895**, *17*, 187 and references cited therein.

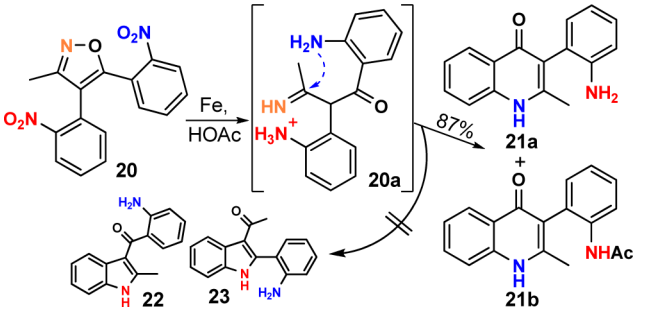
(14) HRMS calculated for **12** $[C_{15}H_{12}N_2O + H]^+$, 237.1022; found, 237.1030. HRMS results along with NMR spectra confirmed the identity of **12**. Fortunately, **13** has one less proton ($[M + H]^+$: 236.1182) leading to the conclusion that one product was formed exclusively.

(15) The results of quantum chemical calculations on model systems can be found in the SI.

Scheme 5. H−H Chemistry of 3,4-Bis(2-nitrophenyl)isoxazole



Scheme 6. H−H Chemistry of 4,5-Bis(2-nitrophenyl)isoxazole



this prediction, **20** was synthesized by condensation of *N*-hydroxyacetimidoyl chloride onto 1,2-bis(2-nitrophenyl)ethanone (NaH in dry THF). Fe/HOAc reduction of **20** proceeded to give quinolin-4(1*H*)-ones **21a** and **21b** (87% total yield) in a 1:1.1 ratio, respectively, confirming formation of acetic anhydride *in situ*.[13] Importantly, indoles **22** and **23** were not obtained as their formation is precluded by formation of the protonated red aniline NH_2 in **20a**.

Since the assignment of structure **21a** was complicated by the expectation that **22** and **23** would have similar NMR spectra and the same mass, chemical shift calculations (using the multistandard approach)[16] were performed using DFT[17] (see SI for details). Mean absolute deviations (MAD) of the chemical shifts relative to experimental data were 0.2, 0.4, and 0.6 ppm (**21a**, **22**, and **23** respectively) for ^{1}H NMR. The MAD for the ^{13}C NMR were 2.8, 4.8, and 4.8 ppm, respectively.[18] The MAD for structure **21a** are the lowest and within the range typically found for correctly assigned structures,[16] suggesting that **21a** is indeed the product of the reduction.[19]

In this work, we have shown that Fe/HOAc reduction of (2-nitrophenyl)- and bis(2-nitrophenyl)isoxazoles leads with great chemoselectivity to a variety of useful heterocycles via heterocycle−heterocycle (**H−H**) transformations. Although the reactivities of the systems described above are influenced by many factors, often juxtaposed in effect, two empirical guidelines for predicting the products in these systems have emerged: (1) chemoselective heterocyclization onto the imine carbon is preferred unless it is deactivated; (2) in systems with competing aniline moieties, the less basic NH_2 is the favored nucleophile. These guidelines will, no doubt, prove useful in facilitating the design of additional **H−H** synthetic reactions of this type.

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Supporting Information Available. Experimental procedures, full spectroscopic data for all new compounds, and X-ray crystallographic data for **8b**, **10a**, and **10b**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(16) Lodewyk, M.; Siebert, M. R.; Tantillo, D. J. *Chem. Rev.* **2012**, *112*, 1839.
(17) Frisch, M. J. *Gaussian 09* (revision B.01): See SI for full author list.
(18) Figures are in the SI.
(19) Typical 3-acylindole ^{13}C C=O shifts are ~190 ppm, while quinolin-4-ones are ~175 ppm. The carbonyl shift from the reduction of 4,5-bis(2-nitrophenyl)isoxazole was 175.0 giving further evidence that quinolin-4-one **21a** was formed in the reduction. For indole related examples, see: (a) Stokes, B. J.; Liu, S.; Driver, T. G. *J. Am. Chem. Soc.* **2011**, *113*, 4702. (b) Guchhait, S. K.; Kashyap, M.; Kamble, H. *J. Org. Chem.* **2011**, *76*, 4853. For quinolin-4-one related examples, see: (c) Cross, R. M.; Manetsch, R. *J. Org. Chem.* **2010**, *75*, 8654. (d) Luo, F. T.; Ravi, V. K.; Xue, C. *Tetrahedron* **2006**, *62*, 9365.