Synthesis of Polycyclic Imidazolidinones via Amine Redox-Annulation
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Supporting Information

ABSTRACT: α-Ketoamides undergo redox-annulations with cyclic secondary amines, such as 1,2,3,4-tetrahydroisoquinoline, pyrrolidine, piperidine, and morpholine. Catalytic amounts of benzoic acid significantly accelerate these transformations. This approach provides polycyclic imidazolidinone derivatives in typically good yields.

Imidazolidinones are frequently encountered as substructures of natural products and synthetic, biologically active compounds (Figure 1).1−3 Among the most common methods used to build the imidazolidinone motif are condensations of α-aminoacetamide derivatives with aldehydes or ketones, various cycloadditions, ring expansions, and others.1 Methods have also emerged that are particularly suitable for the preparation of ring-fused imidazolidinones (Scheme 1). One such approach involves an oxidative intramolecular coupling of α-aminoacetamide derivatives (eq 1).‡ A decarboxylative strategy involving the condensation of proline with α-ketoamides to build bicyclic imidazolidinones containing a pyrrolidine ring has also been established (eq 2).5,6 Here we report a redox-neutral annulation approach to polycyclic imidazolidinones (eq 3).15

Scheme 1. Selected Routes to Polycyclic 4-Imidazolidinones

Oxidative Approach:

Decarboxylative Approach:

Redox-Annulation (this work):

Figure 1. Selected 4-imidazolidinones.
isolation of desired product 2a as a single diastereomer in 50% yield (entry 1). Utilization of catalytic amounts of benzoic acid (20 mol %) resulted in a significant improvement (entry 2). Complete consumption of 1a was observed within 7 h, and 2a was obtained in 95% yield. Replacement of benzoic acid with either acetic acid or 2-ethylhexanoic acid (2-EHA) facilitated the formation of 2a in similar yields but required prolonged reaction times (entries 3 and 4). A reaction that was performed at 50 °C remained incomplete after 44 h and led to product in moderate yield (entry 5). A reduction of the amount of THIQ to 1.5 equiv was well tolerated (entry 6), whereas further reduction to 1.2 equiv led to a slight drop in yield (entry 7). Notably, the reaction performed equally well in the absence of molecular sieves (entry 8).

The scope of the redox-annulation was explored under the optimized conditions of Table 1 (entry 8). A range of α-ketoamides with different substitution patterns were investigated (Scheme 2). The corresponding 4-imidazolidinone products 2 were isolated in good to excellent yields. Both aromatic and aliphatic substituents on the amide nitrogen were tolerated. Likewise, nonenolizable and enolizable α-ketoamides participated in the annulation reaction. In the case of the primary amide-derived product 2n, which was obtained in 53% yield, a competing pathway was identified. Specifically, the corresponding transamidation product was obtained in 38% yield.16 An enantiomerically pure α-ketoamide, derived from (S)-1-phenylethan-1-amine, provided product 2o in 86% yield as a 1.3:1 mixture of diastereomers.

The scope of the amine component is summarized in Scheme 3. Benzylc amines other than THIQ, including the sterically hindered 1-phenyl-THIQ, readily formed annulation products upon reaction with α-ketoamide 1a. Amines with attenuated reactivities, such as pyrrolidine and azepane, provided 4-imidazolidinone products in good yields. Particularly challenging substrates such as piperidine, morpholine, and thiomorpholine underwent the title reaction at elevated temperatures.

As shown in Schemes 2 and 3, reactions involving THIQ, related benzylc amines, and pyrrolidine underwent redox-annulations with α-ketoamides in highly diastereoselective fashion. In contrast, reactions with azepane, piperidine, morpholine, and thiomorpholine were poorly diastereoselective. We suspected that the aminal stereogenic center might be configurationally unstable under the reaction conditions. Thus, product ratios may reflect the different thermodynamic stabilities of the two diastereomers. To test this hypothesis,

### Table 1. Evaluation of Reaction Conditions

| entry | THIQ (equiv) | catalyst | time (h) | yield (%) |
|-------|--------------|----------|----------|-----------|
| 1     | 2            |          | 48       | 50        |
| 2     | 2            | PhCOOH   | 7        | 95        |
| 3     | 2            | AcOH     | 23       | 92        |
| 4     | 2            | 2-EHA    | 21       | 91        |
| 5     | 2            | PhCOOH   | 44       | 56        |
| 6     | 1.5          | PhCOOH   | 12       | 88        |
| 7     | 1.2          | PhCOOH   | 12       | 88        |
| 8     | 1.5          | PhCOOH   | 15       | 85        |

*a* Reactions were performed on a 0.2 mmol scale. All yields correspond to isolated yields, dr >25:1 in all cases. *b* Reaction was run at 50 °C and remained incomplete. *c* Without 4 Å MS.

### Scheme 2. Ketoamide Scope

Reactions were performed on a 0.5 mmol scale. All yields correspond to isolated yields. Transamidation product (1-(3,4-dihydroisoquinolin-2(1H)-yl)-2-phenylethane-1,2-dione) was obtained in 38% yield.

### Scheme 3. Amine Scope

Reactions were performed on a 0.5 mmol scale. All yields correspond to isolated yields. *a* Reaction was performed in PhMe (0.25 M) under microwave irradiation for 30 min at 220 °C. *b* Reaction was performed in PhMe (0.25 M) under microwave irradiation for 1 h at 220 °C.
the readily available pure diastereomers of product 3g were exposed to the reaction conditions (eqs 4 and 5). Upon extended heating, both mixtures converged to a final 2:1:1 ratio of diastereomers. These experiments establish that product isomerization can indeed occur under the reaction conditions.

Two plausible mechanistic scenarios are shown in Scheme 4, depicting pyrrolidine and α-ketoamide 1a as prototypical examples. Based on previous investigations, the initial formation of N,O-acetal 4 appears highly likely. Again based on precedent, 4 could lose benzoic acid to form azomethine ylide 5. Following the general mechanism of other redox-annulations, 5 could reengage benzoic acid to form N,O-acetal 6. The latter ultimately undergoes ring closure to final product 3e with loss of benzoic acid, possibly via the zwitterionic intermediate 7 (pathway A). In an alternate scenario, conjugated azomethine ylide 8 undergoes ring closure in what is formally a 1,5-electrocyclization. The resulting intermediate 9 then undergoes tautomerization to product 3e (pathway B).

In conclusion, we have achieved high-yielding syntheses of polycyclic imidazolidinones via redox-annulations of cyclic amines with a range of α-ketoamides. These reactions are efficiently catalyzed by benzoic acid and are rare examples of redox-neutral transformations in which an amine α-C−H bond is replaced by a C−N bond in the context of five-membered ring formation.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03309.

Experimental procedures and characterization data, including X-ray crystal structures of products 2a and 3d (PDF)
X-ray data for compound 2a (CIF)
X-ray data for compound 3d (CIF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Review on the synthetic and medicinal chemistry of 4-imidazolidinones: Blackmore, T.; Thompson, P. Heterocycles 2011, 83, 1953.
(2) For a general review on the synthesis of aminal-type structures, see: Hierssemann, M. In Comprehensive Organic Functional Group Transformations II; Katritzky, A. R. T., Richard, J. K., Ed.; Elsevier Ltd.: Oxford, UK, 2005; Vol. 4, p 411.
(3) Selected reports on natural and synthetic, biologically active 4-imidazolidinones: (a) Smissman, E.; Inloes, R.; El-Antably, S.; Shaffer, P. J. Med. Chem. 1976, 19, 161. (b) Leysen, J.; Gommeren, W.; Laduron, P. Biochem. Pharmacol. 1978, 27, 307. (c) Nelson, D.; Taylor, E. Eur. J. Pharmacol. 1986, 124, 207. (d) Nikam, S.; Martin, A. S.; Nelson, D. J. Med. Chem. 1988, 31, 1965. (e) Rasmussen, G.; Bundgaard, H. Int. J. Pharm. 1991, 71, 45. (f) Pinza, M.; Farina, C.; Cerri, A.; Pfeiffer, U.; Riccaboni, M. T.; Banfi, S.; Biagetti, R.; Pozzi, O.; Magnani, M.; Dorigotti, L. J. Med. Chem. 1993, 36, 4214. (g) Thomsen, C.; Hohweg, R. Br. J. Pharmacol. 2000, 131, 903. (h) Izzendoorn, D. R.; Botman, P. N. M.; Blauw, R. H. Org. Lett. 2006, 8, 239. (i) Toumi, M.; Couty, F.; Marrot, J.; Eano, G. Org. Lett. 2008, 10, 5027. (j) Vale, N.; Prudencio, M.; Marques, C.; Collins, M.; Gut, J.; Nogueira, F.; Rosenthal, P.; Cushion, M.; Rosario, V.; Mota, M.; Moreira, R.; Gomes, P. J. Med. Chem. 2009, 52, 7800. (k) Vale, N.; Nogueira, F.; Rosario, V.; Gomes, P.; Moreira, R. Eur. J. Med. Chem. 2009, 44, 2506.
(4) (a) Vasvari-Debreczy, L.; Beckett, A.; Vutthikongsirigool, W. Tetrahedron 1981, 37, 4337. (b) Papadopoulos, A.; Lewall, B.; Steckhan, E.; Ginzel, K.; Knoch, F.; Nieger, M. Tetrahedron 1991, 47, 563. (c) Yu, H.; Shen, J. RSC Adv. 2015, 5, 9815. (d) Ren, X.; O’Hanlon, J.; Morris, M.; Robertson, J.; Wong, L. ACS Catal. 2016, 6, 6833.
(5) (a) Wu, J.; Jiang, H.; Yang, J.-g.; Jin, Z.-n.; Chen, D.-b. Tetrahedron Lett. 2017, 58, 546.
(6) Examples of condensation-based approaches to polycyclic 4-imidazolidinones: (a) Katritzky, A. R.; He, H.-Y.; Wang, J. J. Org. Chem. 2002, 67, 4951. (b) Ferrari, R.; Gomes, J. R. B.; de Oliveira, E.; Moreira, R.; Gomes, P. J. Org. Chem. 2007, 72, 4189.
(7) (a) Zhang, C.; De, C. K.; Mal, R.; Seidel, D. J. Am. Chem. Soc. 2008, 130, 416. (b) Zhang, C.; Das, D.; Seidel, D. Chem. Sci. 2011, 2, 233. (c) Dieckmann, A.; Richers, M. T.; Platonova, A. Y.; Zhang, C.; Seidel, D.; Houk, K. N. J. Org. Chem. 2013, 78, 4132. (d) Richers, M. T.; Deb, I.; Platonova, A. Y.; Zhang, C.; Seidel, D. Synthesis 2013, 45, 1730. (e) Richers, M. T.; Breugst, M.; Platonova, A. Y.; Ulrich, A.; Dieckmann, A.; Houk, K. N.; Seidel, D. J. Am. Chem. Soc. 2014, 136, 6123. (f) Jarvis, C. L.; Richers, M. T.; Breugst, M.; Houk, K. N.; Seidel, D. Org. Lett. 2014, 16, 3556. (g) Kang, Y.; Chen; Breugst, M.; Seidel, D. J. Org. Chem. 2015, 80, 9628. (h) Ma, L.; Seidel, D. Chem. - Eur. J. 2015, 21, 12908. (i) Chen, W.; Seidel, D. Org. Lett. 2016, 18, 1024. (j) Zhu, Z.; Seidel, D. Org. Lett. 2017, 19, 2841.

(8) (a) Zheng, L.; Yang, F.; Dang, Q.; Bai, X. Org. Lett. 2008, 10, 889. (b) Mahato, S.; Haque, M. A.; Diwari, S.; Jana, K. C. RSC Adv. 2014, 4, 46214. (c) Li, J.; Qin, C.; Yu, Y.; Fan, H.; Fu, Y.; Li, H.; Wang, W. Adv. Synth. Catal. 2017, 359, 2191. (d) Li, J.; Fu, Y.; Qin, C.; Yu, Y.; Li, H.; Wang, W. Org. Biomol. Chem. 2017, 15, 6474.

(9) Selected reviews on amine α-C–H functionalization, including redox-neutral approaches: (a) Murahashi, S.-I. Angew. Chem., Int. Ed. Engl. 1995, 34, 2443. (b) Matysus; P.; Elias, O.; Tapolciansky, P.; Polonka-Balint, A.; Halasz-Dajka, B. Synthesis 2006, 2006, 2625. (c) Campos, K. R. Chem. Soc. Rev. 2007, 36, 1069. (d) Murahashi, S.-I.; Zhang, D. Chem. Soc. Rev. 2008, 37, 1490. (e) Li, C.-J. Acc. Chem. Res. 2009, 42, 335. (f) Jazarz, R.; Hilte, J.; Renaudat, A.; Sofack Kreutzer, J.; Baudoin, O. Chem. - Eur. J. 2010, 16, 2654. (g) Yeung, C. S.; Dong, V. M. Chem. Rev. 2011, 111, 1215. (h) Pan, S. C. Beilstein J. Org. Chem. 2012, 8, 1374. (i) Mitchell, E. A.; Peschiulli, A.; Lefere, N.; Meepoor, L.; Maes, B. U. W. Chem. - Eur. J. 2012, 18, 10092. (j) Zhang, C.; Tang, C.; Jiao, N. Chem. Soc. Rev. 2012, 41, 3464. (k) Jones, K. M.; Klussmann, M.; Synlett 2012, 12, 159. (l) Beng, P.; Mould, N. Chem. - Eur. J. 2013, 19, 13274. (m) Platonova, A. Y.; Gliukhareva, T. V.; Zimovets, O. A.; Morzherin, Y. Y. Chem. Heterocycl. Compd. 2013, 49, 357. (n) Priester, C. K.; Rankic, D. A.; MacMillan, D. W. C. Chem. Rev. 2013, 113, 5322. (o) Girard, S. A.; Knauber, T.; Li, C.-J. Angew. Chem., Int. Ed. 2014, 53, 74. (p) Halbach, M. C.; Seidel, D. Angew. Chem., Int. Ed. 2014, 53, 1010. (q) Wang, L.; Xiao, J. Adv. Synth. Catal. 2014, 356, 1137. (r) Vo, C.-Y. T.; Bode, J. W. J. Org. Chem. 2014, 79, 2809. (s) Seidel, D. Org. Chem. Front. 2014, 1, 426.

(10) Selected reviews on various types of redox-neutral transformations: (a) Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. Angew. Chem., Int. Ed. 2009, 48, 2854. (b) Mahatthanachai, J.; Bode, J. W. Angew. Chem. 2014, 47, 696. (c) Ketcham, J. M.; Shin, L.; Montgomery, T. P.; Kirsch, M. J. Angew. Chem., Int. Ed. 2014, 53, 9142. (d) Huang, H.; Ji, X.; Wu, W.; Jiang, H. Chem. Soc. Rev. 2015, 44, 1155.

(11) For detailed discussions on the mechanisms of these transformations, see refs 7c–e and 9g and the following reports: (a) Xing, Y.; Yu, A.; Cheng, J. Org. Lett. 2011, 13, 6054. (b) Ma, L.; Paul, A.; Breugst, M.; Seidel, D. Chem. - Eur. J. 2016, 22, 18179.

(12) Examples of redox-neutral α-C–H functionalizations of secondary amines in the context of (3 + 2) cycloadditions: (a) Ardlil, H.; Grigg, R.; Sridharan, V.; Sureshrakumar, S.; Thianpattanagul, S.; Kanujan, S. J. Soc. Chem. Chem. Commun. 1986, 602. (b) Ardlil, H.; Dorrity, M. R. J.; Grigg, R.; Leon-Ching, M. S.; Malone, J. P.; Sridharan, V.; Thianpattanagul, S. Tetrahedron 1990, 46, 6435. (c) Ardlil, H.; Fontaine, X. L. R.; Grigg, R.; Henderson, D.; Montgomery, J.; Sridharan, V.; Sureshrakumar, S. Tetrahedron 1990, 46, 6449. (d) Wang, J.; Metes, M. P.; Metes, K. B.; Takusagawa, F. Tetrahedron Lett. 1990, 31, 5543. (e) Wittland, C.; Arend, M.; Risch, N. Synthesis 1996, 1996, 367. (f) Marx, M. A.; Grillot, A.-L.; Louer, C. T.; Beaver, K. A.; Bartlett, P. A. J. Am. Chem. Soc. 1997, 119, 6153. (g) Grigg, R.; Sridharan, V.; Thornton-Pett, M.; Wang, J.; Xu, J.; Zhang, J. Tetrahedron 2002, 58, 2627. (h) Parmar, N. J.; Pansuriya, B.; Labana, B. M.; Kent, R.; Gupta, V. K. RSC Adv. 2013, 3, 17527. (i) Rahman, M.; Bagdi, A. K.; Mishra, S.; Hajra, A. Chem. Commun. 2014, 20, 591. (j) Mantelung, K.; Lin, Y.; Seidel, D. Org. Lett. 2014, 16, 5910. (k) Pavan Kumar, C. S.; Harsha, K. B.; Mantelung, K.; Ranagoppa, K. S. RSC Adv. 2015, 5, 16166. (l) Safaei-Gholami, J.; Masoomi, R. RSC Adv. 2015, 5, 15911. (m) Yang, H.-T.; Tao, Y.-C.; Gai, J. W.; Li, J.; X. Y.; Liu, K. N.; Seidel, D. Org. Lett. 2014, 16, 3556.