Diels−Alder Construction of Regiodifferentiated meta-Amino Phenols and Derivatives

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*Supporting Information

ABSTRACT: Synthetic access to regiodifferentiated meta-amino phenols is described. The strategy relies upon distinct deprotonation conditions to afford regioisomeric thermodynamic and kinetic dienes that undergo a tandem Diels−Alder and retro-Diels−Alder sequence with assorted acetylenic dienophiles to afford a range of aromatic products. meta-Amino phenol (m-APhOH) and meta-amino pyridinol (m-APyOH) derivatives are important building blocks for natural product synthesis. They have proven themselves as privileged pharmaceutical scaffolds1 and serve as inhibitors of JNK2 and CGRP,3 modulators of the delta-opioid receptor,4 and efficacious treatment for neurological and psychiatric maladies,5 Alzheimer’s disease,6 and various carcinomas.7 However, differentially substituted m-APhOHs and m-APyOHs, particularly those displaying electron-deficient amino functionality, are tedious to construct by aryl nitration−reduction−protection regimes, palladium mediated cross-coupling sequences,8 and other strategies,9 such as conventional Diels−Alder sequences.10

Herein, we report a new strategy to secure these important aromatic materials by way of a regioselective deprotonation of various cyclic vinylogous amides, a plan loosely based upon Danishefsky’s preliminary observations regarding the synthesis of pseudo-symmetric resorcinylc materials.11

Our process enables rapid access to regiodifferentiated aromatic materials using two isomeric dienes derived from a common cyclic vinylogous amide and uncovers equilibria between the resulting dienes, which has often been overlooked.12 The skeletons of our regiosymmetric aromatic products are found in compounds resembling tetrapetalone A (1) and the CGRP inhibitor (2) (Figure 1).1,3,3

Cyclic vinylogous amides (5a–c, Table 1) were prepared by condensation of the appropriate 1,3-cyclohexadione (3a–3c) with benzyl amine and acylation with benzyl chloroformate.14 Our process continued with regioselective deprotonation of the

| entry | CVA kinetic diene (k-D) | thermodynamic diene (t-D) | deprotonation method ratio k-D/t-D |
|-------|----------------|----------------|---------------------|
| 1a,b,d | 5a 6a 7a | C, 2:1:1 | <1:20 |
| 2a,b,d | 5a 6a 7a | A, 1:2:1 | >10:1 |
| 3b | 5b 6b 7b | A, 1:2:1 | <1:20 |
| 4b | 5b 6b 7b | B, 1:2:1 | <1:20 |
| 5b | 5c 6c 7c | B, 1:2:1 | >10:1 |

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vinyllogous amides (5a−c, Table 1) to form either the thermodynamic or the kinetic enolate.15 Enolate interception with TBSCI furnished the corresponding dienes (7a−c, 6a−c, Table 1). For example, vinyllogous amide 5a was subjected to deprotonation with KHMS under kinetic enolization conditions. Addition of TBSCI afforded the diene (7a) as the sole product (Table 1, entry 1), which proved stable for over a month when frozen in benzene. Deprotonation of 5a with KHMS under kinetic enolization conditions and addition of TBSCI afforded the diene (6a) in an ∼7:1 ratio of 6a:7a. However, Schlosser’s conditions (n-BuLi, KOT-Bu) reproducibly increased the ratio to >10:1, despite a lower yield (Table 1, entry 2).16 We sought to improve the kinetic/thermodynamic diene ratio by varying the Y and Y’ substituents using vinyllogous amides 5b and 5c. While thermodynamic dienes (7b−c) formed selectively as before (Table 1, entries 3, 5), the selectivity for kinetic dienes (6b−c) failed to improve (Table 1, entries 4, 6). We envisioned that submission of these respective regioisomers resulting from the thermodynamic or the kinetic enolate.15 Enolate interception with assorted dienophiles to a mixture was obtained. The major product, 15a, arose from the ketone acting as the predominant directing group (15a:15b, 2:1). Remarkably, ethyl cyanoformate proceeded to a core widely found as the corresponding pyridone in natural and synthetic products.3 Additional chemical manipulations further demonstrate the utility of these new aromatic materials (Scheme 2). Hydrogenolysis of bis-protected m-APyOH 8 provided the aniline 18 in 96% yield, while stirring m-APyOH 12 with acid afforded the pyridone 19 in 90% yield.19

Substitution of the individual kinetic dienes (6a−c, Table 1) to similar thermal conditions with excess DMAD dienophile gave the anticipated product 20. However, a significant amount of undesired regioisomer 8, resulting from diene 7a, was also isolated. Isomeric ratios among the phenol products were nearly identical for dienes 6a−c. As done in the thermodynamic case, we chose to focus on diene 6a, which was submitted to the same reaction conditions as diene 7a with a similar assortment of acetylenes (Table 3). Despite a starting diene ratio of >10:1, 6a:7a, two isomeric products always formed: the expected products (20−24) from the kinetic diene 6a, and their respective regioisomers resulting from the thermodynamic diene 7a. Since the product ratios failed to reflect the initial diene ratio, we suspected that perhaps the regioisomeric dienes undergo reaction at different rates or that the ratio of 6a:7a

| entry | dienophile | thermodynamic product | yield* |
|-------|------------|-----------------------|-------|
| 1     |            | 7a                    | 85%   |
| 2     |            | 7a                    | 85%   |
| 3     |            | 7a                    | 85%   |
| 4     |            | 7a                    | 79%   |
| 5     |            | 7a                    | 65%   |
| 6     |            | 7a                    | 40%   |
| 7     |            | 7a                    | 33%   |
| 8     |            | 7a                    | 67%   |
| 9     |            | 7a                    | 61%   |

*Reaction yields based on the diene 7a as the limiting reagent. Dienophile equivalents. a2 equiv. b4 equiv. c10 equiv. dDienophile used without purification. eYield of 14 based on the corresponding isolated phenol, characterized as such. fMixture of regioisomers 15a:15b (2:1); major product 15a pictured. gCombined yield.

Scheme 1. Convergent Closure of Regioisomers 15a and 15b
changes during the course of the reaction. The best outcomes were observed with bis(trifluoroethyl)acetylene dicarboxylate (entry 2) and the propargylic aldehyde (entry 5), which are presumably more reactive dienophiles. Ethyl cyanoformate appeared to undergo successful reaction, but the product proved difficult to isolate. All isolated products (20−24) exhibit hindered rotation about the N−Ar bond due to the steric encumbrance of the neighboring group. Variable temperature experiments demonstrated free rotation, although it was difficult to fully resolve their 13C spectra. A variety of Lewis acids were investigated in an attempt to improve these isomeric ratios. However, in our hands, most caused degradation of the diene to the cyclic vinylogous amide 5a.

Table 3. Cycloadditions with Kinetic Diene 6a

| entry | dienophile | kinetic product | product ratio combined yield |
|-------|------------|----------------|-----------------------------|
| 1′    |            |                | 20:8 2:1, 80%              |
| 2′    |            |                | 21:9 >4:1, 59%             |
| 3′    |            |                | 22:10 >3:1, 73%            |
| 4′    |            |                | 23:11 >1:1, 57%            |
| 6′    |            |                | 24:12 >4:1, 41%            |

− Diene ratio was >10:1 6a:7a. − Reaction yields based on the diene 6a as the limiting reagent. Dienophile equivalents. − 2 equiv. − 4 equiv. − Characterized as the corresponding phenol.

To better understand the apparent isomerization, a deuterated system was synthesized (Scheme 3). Diene 6d was prepared by repetitive formation of 7a and deuteration of the intermediate thermodynamic siloxydiene with acetic acid-d4 to enrich the γ-position, which eventually resulted in 80% deuterium incorporation for 6d. Upon heating, the non-deuterated diene 6a had been found to equilibrate from >10:1 to 7:1 over 24 h to 5:1 over 3 days, and to 2:1 over 7 days. However, under strictly thermal conditions, the deuterated diene 6d did not behave similarly to afford diene 7d (Scheme 3). Upon heating the deuterated diene 6d with the acetylenic dienophile DMAD, aromatics 20 and 8d arose in a 2:1 ratio by analysis of the crude NMR. This suggests that the dienophile might facilitate the formation of 7d perhaps via a charge-transfer complex, or zwitterionic intermediate. However, this notion was not probed further.

To establish the tolerance and utility of this strategy, we prepared the sophisticated diene derivative 25 in six steps and 12% yield from dimedone 3a, using a mild SmI2-mediated cyclization recently developed in our lab to construct the methylated tetramic acid (Scheme 4). Application of our standard thermal conditions to a mixture of diene 25 and DMAD afforded the anticipated aromatic compound, which was desilylated by prolonged heating or exposure to fluoride and afforded compound 26a along with its minor regioisomer (not pictured) (2:1) in an 85% combined yield.

This work demonstrates that dimedone 3a can be used to prepare a plethora of highly functionalized m-APhOHs and m-APyOH. This strategy is tolerant of a wide range of nitrogen appended functional groups that would not be amenable to preparation by any other existing method.

**ASSOCIATED CONTENT**

## Supporting Information

Experimental procedures and characterization data for all new compounds and experimental procedures for all noncommercial dienophiles. This material is available free of charge via the Internet at http://pubs.acs.org.

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**Notes**

The authors declare no competing financial interest.
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REFERENCES

(1) (a) Yang, Z.-Q.; Geng, X.; Solit, D.; Pratillas, C. A.; Rosen, N.; Danishefsky, S. J. Am. Chem. Soc. 2004, 126, 7881–7889. (b) Chen, H. C.; Bai, J.; Fang, Z.-F.; Yu, S.-S.; Ma, S.-G.; Xu, S.; Li, Y.; Qu, J.; Ren, J.-H.; Li, L.; Si, Y.-K.; Chen, X.-G. J. Nat. Prod. 2011, 74, 2438–2445. (c) Dupuis, S. N.; Veintot, T.; Monsoro, S. M. A.; Douglas, S. E.; Svititsky, R. T.; Goralski, K. B.; McFarland, S. A.; Jakeman, D. L. J. Nat. Prod. 2011, 74, 2420–2424.

(2) Zhao, J.; Serby, M. D.; Xin, Z.; Szczepankiewicz, B. G.; Liu, M.; Kosogof, C.; Lu, B.; Nelson, L. T. J.; Johnson, E. F.; Wang, S.; Pederson, T.; Gumb, R. J.; Clampit, J. E.; Haasch, D. L.; Abad-Zapatero, C.; Fry, E. H.; Rondinone, C.; Trevillian, J. M.; Sham, H. L.; Liu, G. J. Med. Chem. 2006, 49, 4455–4458.

(3) Gottschling, D.; Dahmann, G.; Dooods, H.; Heiman, A.; Mueller, S. G. U.S. Patent 065921 A1, 2009.

(4) (a) Carson, J. R.; Boyd, R. E.; Neilson, L. A. W.O. Patent 46191 A1, 2001. (b) Boyd, R. E.; Reitz, A. W. O. Patent 05557 A2, 2004.

(5) Aicher, T. D.; Cortez, G. S.; Groendedyk, T. M.; Khilevich, A.; Knobelsdorf, J. A.; Marmasater, F. P.; Schkeryantz, J. M.; Tang, T. P. U.S. Patent 7 678 794 B2, 2010.

(6) (a) Galley, G.; Goergerl, A.; Zbinden, K. G.; Norcross, R.; Stalder, H. U.S. Patent 0096906 A1, 2008. (b) Scopes, D. I. C.; Horwell, D. C. U.S. Patent 0298325 A1, 2010.

(7) (a) Bedin, M.; Gaben, A.-M.; Saucier, C.; Mester, J. J. Org. Chem. 2004, 109, 643–652. (b) Lumma, W. C. Jr.; Smith, A. M.; Sisko, J. T. J. Am. Chem. Soc. 1999, 121, 1873. (b) Bronner, S. M.; Mackey, J. L.; Houk, K. N.; Garg, N. K. J. Am. Chem. Soc. 2012, 134, 13966–13969. (c) Bronner, S. M.; Goetz, A. E.; Garg, N. K. J. Am. Chem. Soc. 2011, 133, 3832–3835.

(10) Rawal: (a) Kozmin, S. A.; Rawal, V. H. J. Org. Chem. 1997, 62, 5520–5523. Pada; (b) Pada, D.; Kissell, W. S.; Eidel, C. K. Can. J. Chem. 2001, 79, 1681–1693. (c) Padwa, A.; Dimitroff, M.; Waterson, A. G.; Wu, T. J. Org. Chem. 1997, 62, 4088–4096. Carter: (d) Ashburn, B. O.; Carter, R. G. J. Org. Chem. 2007, 72, 10220–10223; see Supporting Information for a brief summary.

(11) (a) Geng, X.; Danishefsky, S. J. Org. Lett. 2004, 6, 413–416. (b) Yoshino, T.; Ng, F.; Danishefsky, S. J. Am. Chem. Soc. 2006, 128, 14185–14191. (c) Dai, M.; Sarlah, D.; Yu, M.; Danishefsky, S. J.; Jones, G. O.; Houk, K. N. J. Am. Chem. Soc. 2007, 129, 645–657. (d) (a) Morrison, C. F.; Burnell, D. J. Tetrahedron Lett. 2001, 42, 7367–7369. (b) Buckele, R. N.; Burnell, D. J. Tetrahedron 1999, 55, 14829–14838. (c) Blanco, L.; Slougui, N.; Rousseau, G.; Conia, J. M. Tetrahedron Lett. 1981, 22, 265–268.

(13) Isolation and characterization: (a) Komoda, T.; Sugiyama, Y.; Naoki, A.; Imachi, M.; Hirota, H.; Hirota, A. Tetrahedron Lett. 2003, 44, 1659–1661. (b) Komoda, T.; Sugiyama, Y.; Abe, N.; Imachi, M.; Hirota, H.; Koshino, H.; Hirota, A. Tetrahedron Lett. 2003, 44, 7417–7419. Synthetical efforts: (c) Wang, X.; Porco, J. A. Jr. Angew. Chem. Int. Ed. 2005, 44, 3067–3071. (d) Corrigenda: Wang, X.; Porco, J. A., Jr. Angew. Chem. Int. Ed. 2006, 45, 6607. (e) Marcus, A. P.; Sarpong, R. Org. Lett. 2010, 12, 4560–4563. (f) Li, C.; Li, X.; Hong, R. Org. Lett. 2009, 11, 4036–4039. (g) Vaidya, T.; Cheng, R.; Carlsen, P. N.; Frontier, A. J.; Eisenberg, R. Org. Lett. 2014, 16, 800–803.

(14) Edafiofo, I. O.; Hinko, C. N.; Chang, H.; Moore, J. A.; Mulzac, D.; Nicholson, J. M.; Scott, K. R. J. Med. Chem. 1992, 35, 2798–2805.