Published in final edited form as:

Chemistry. 2015 September 7; 21(37): 12908–12913. doi:10.1002/chem.201501667.

Intramolecular Redox-Mannich Reactions: Facile Access to the Tetrahydropyprotoberberine Core

Mr. Longle Ma^a and Prof. Dr. Daniel Seidel^{a,*}

^a

Abstract

Cyclic amines such as pyrrolidine undergo redox-annulations with 2-formylaryl malonates. Concurrent oxidative amine α -C–H bond functionalization and reductive *N*-alkylation render this transformation redox-neutral. This redox-Mannich process provides regioisomers of classic Reinholdt reaction products as an entry to the tetrahydropyprotoberberine core, enabling the synthesis of ($\pm$)-thalictrovine and its epimer. An unusually mild amine-promoted dealkoxycarbonylation was discovered in the course of these studies.

Keywords

C–H functionalization; redox-neutral; azomethine ylides; heterocycles

The Reinholdt reaction is a classic example of a redox-neutral amine α -C–H bond functionalization process and is thought to occur via a 1,5-hydride shift/Mannich-type ring-closure sequence (e.g., **1** $\rightarrow$ **2**, Scheme 1).^[1] First reported in 1984, this and related transformations have recently experienced a renewed and continuously growing interest.^[2,3] This is in line with the general trend towards developing new transformations that minimize the generation of unwanted byproducts by virtue of being redox-neutral.^[4] While the majority of methods for amine α -C–H bond functionalization typically utilize tertiary amines as starting materials,^[2,5] our group has recently advanced a general concept for the redox-neutral C–H functionalization of secondary amines.^[6] This complementary approach effectively combines a reductive *N*-alkylation with an oxidative α -functionalization and involves azomethine ylides^[7] as reactive intermediates.^[8] The concept has been further extended to redox-neutral β -C–H bond functionalization via the intermediacy of enamines.^[9] Here we report a method that provides access to constitutional isomers of Reinholdt reaction products, differing only in the position of a methylene bridge. Products **4**, obtained via intramolecular redox-Mannich reaction of **3** with 1,2,3,4-tetrahydroisoquinoline (THIQ), possess the core structure of the tetrahydropyprotoberberine family of natural products.^[10]

We initiated our investigation of the proposed intramolecular redox-Mannich reaction by employing malonate-aldehyde **3a**^[11] and pyrrolidine as the model substrates (eq 1). Accordingly, **3a** was exposed to three equivalents of pyrrolidine in ethanol under reflux, conditions that were previously developed for the formation of aminals from *ortho*-

aminobenzaldehydes and pyrrolidine.^[6b] Following a reaction time of three hours during which **3a** was consumed fully, a complex mixture of unidentified polar materials was formed and none of the desired product **5a** was observed. Instead, the unexpected dealkoxycarbonylated product **6** was formed in 25% yield (*vide infra*).

(1)

Conditions that were shown previously to be applicable to a wider range of amine redox-transformations were examined next, namely the use of toluene as the solvent and carboxylic acids as additives (Table 1).^[6a] Exposure of **3a** and pyrrolidine (1.3 equiv) to reflux in toluene in the absence of any additives led to the consumption of **3a** within 12 hours (entry 1). As observed before, a complex mixture of unidentified polar materials was observed. Nevertheless, the desired product **5a** was obtained, albeit in only 5% yield. In addition, dealkoxycarbonylated product **6** was isolated in 8% yield. A dramatically different reaction outcome was observed in the presence of 20 mol% of acetic acid (entry 2). Complete consumption of malonate starting material occurred within four hours and redox-Mannich product **5a** was formed in 39% yield. Further reduction of the reaction time and increase in yield of **5a** to 53% was achieved with one equivalent of acetic acid (entry 3). In this instance, byproduct **7** was isolated in 18% yield, a compound formally resulting from the reaction of **5a** with **6** (*vide infra*). A further increase of the amount of acetic acid to ten equivalents led to the isolation of **5a** in 68% yield, accompanied by the formation of **7** in 15% yield (entry 5). Replacement of acetic acid for 2-ethylhexanoic acid (2-EHA) resulted in the clean formation of **5a** in 76% yield and only trace amounts of **7** (entry 6). Similar results were obtained with five instead of ten equivalents of 2-EHA (entry 7). The use of other carboxylic acid promoters or the application of microwave conditions did not result in any further improvements (entries 8–11).

The optimized conditions were subsequently applied in reactions of various malonate-aldehydes with pyrrolidine (Scheme 2). Starting materials with different ester groups participated in this transformation. Ring-substitution with electron-donating or -withdrawing substituents was readily tolerated. Products **5** were isolated in typically moderate to good yields following relatively brief reaction times. Attempts to extend the substrate scope to piperidine met with limited success (eq 2). In order for **3a** to engage in a redox-Mannich reaction with piperidine, higher reaction temperatures were required and the best yield for product **8** was 25%. Under these conditions, a significant amount of competing dealkoxycarbonylation was noted.^[12]

(2)

Redox-Mannich reactions were also conducted with THIQ and related amines, providing products that contain the tetrahydropyprotoberberine core (Scheme 3). As expected, THIQ was found undergo the reaction with **3a** more readily than pyrrolidine. The highest yield of 83% for product **9a** was obtained at 90 °C, using conditions otherwise identical to those utilized in pyrrolidine-based reactions. Substituted THIQ's and tryptoline also underwent the title reaction. Interestingly, the related benzazepane required higher temperatures in order to react with **3a**, yielding **9f** in 43% yield.

It should be noted that the reaction of **3a** with THIQ was very tolerant to deviation from the optimized conditions. In fact, the reaction proceeded even at room temperature, albeit slowly, using only 20 mol% of 2-EHA (eq 3). At the same catalyst loading at 90 °C, product **9a** was isolated in 79% yield following a reaction time of three hours (not shown).¹³

(3)

An attempted redox-Mannich reaction with **3a** and 1-phenyl THIQ took an unexpected course (eq 4). Exposure of these substrates to the standard conditions did not lead to the isolation of any redox-Mannich product. Instead, product **10a** was formed in 70% yield. The formation of this lactam presumably arises from the hydrolysis of an intermediate azomethine ylide or iminium ion by adventitious water, followed by aminolysis of one of the ester groups. This reactivity appears to be general for amines of this type and extends to the use of monoester **6**. Employing the same reaction conditions, a tryptamine-derived starting material gave rise to the formation of product **10b** (eq 5).

(4)

(5)

A number of experiments were performed to shed light on the underlying mechanisms for byproduct formation (Scheme 4). Regarding the formation of β -functionalized product **7**, two scenarios appeared plausible. This product could form either via the reaction of regular redox-Mannich product **5a** with dealkoxycarbonylated starting material **6**, or β -functionalization could take place in a prior step. To determine which of the two pathways is operative, a mixture of **5a** and **6** was exposed to reaction conditions known to facilitate the formation of **7** (c.f. Table 1, entry 3). However, no **7** was isolated in this instance. Similarly, a related experiment in which **6** was exchanged for the more electrophilic *p*-chlorobenzaldehyde failed to provide any detectable amounts of product **11**. In contrast, an experiment in which a 1:1 mixture of malonate-aldehyde **3a** and *p*-chlorobenzaldehyde were allowed to react with pyrrolidine resulted in the isolation of **11** in 29% yield, in addition to **5a** (28% yield). Compound **7** was not observed in this instance. Given these findings, it appears that the competing β -functionalization step occurs prior to the Mannich ring-closure.

The unusual dealkoxycarbonylation process was also investigated further (Scheme 5).^[14] Remarkably, dealkoxycarbonylation of **3a** could be achieved under exceedingly mild conditions. For instance, exposure of **3a** to two equiv of piperidine led to the isolation of dealkoxycarbonylated product **6** in 50% yield following a reaction time of 36 hours at room temperature. The reaction remained incomplete and no trace of **8** was observed. Under otherwise identical conditions, addition of 2-EHA (10 equiv) or use of 2-EHA (10 equiv) by itself did not lead to any observable dealkoxycarbonylation (not shown).^[15] It should be noted that diethyl 2-phenylmalonate (**12**) failed to undergo dealkoxycarbonylation to give ethyl 2-phenylacetate (**13**) under a variety of conditions. In each case, even under more forcing conditions, **12** was recovered unchanged (Scheme 5). These findings indicate, perhaps not surprisingly, that the pendent aldehyde plays a crucial role in the dealkoxycarbonylation process.

A mechanistic rationale accounting for the formation of the main products is presented in Scheme 6. Malonatealdehyde **3a** and pyrrolidine most likely exist in equilibrium with hemiaminal **14**. The latter intermediate can suffer loss of water to form zwitterion **15** which can also be considered as an *ortho*-quinoidal species (resonance structure not shown). Subsequent 1,6-proton transfer results in the formation of azomethine ylide **16**. This species can participate in a second proton transfer step to give zwitterion **17** followed by ring-closure to provide redox-Mannich product **5a**. In analogy to our previous study on the synthesis of benzoxazines,^[6] 2-EHA is likely involved in one if not both proton transfer steps and possibly in the elimination of water during the formation of **15**.

Hemiaminal **14** is also likely involved in the competing dealkoxycarbonylation, a process that could be initiated by the formation of lactone **18** with concurrent elimination of ethanol. Lactone **18** could then fragment into CO₂ and zwitterion **19**. Subsequent hydrolysis of this species would lead to the dealkoxycarbonylation product **6** and pyrrolidine. Azomethine ylide **16**, instead of undergoing intramolecular proton transfer to form **17**, may also be protonated by external acid to form an endocyclic iminium ion or *N,O*-acetal (not shown) that could ultimately be transformed to enamine **20**. This intermediate could engage in an aldol-type reaction with **6** to give **21**. Loss of water and subsequent ring-closure provides a pathway to **7**.

The redox-Mannich reaction was applied in a formal total synthesis of (±)-thalictricavine^[16] and the synthesis of (±)-epi-thalictricavine (Scheme 7).^[17] Commercially available aldehyde **22** was converted into malonate-aldehyde **23** in five steps and 44% overall yield.^[18] The redox-Mannich reaction of **23** with THIQ **24** proceeded smoothly to give annulation product **25** in 87% yield. Hydrolysis of **25** with subsequent decarboxylation provided amino acid **26** as a mixture of diastereomers that was processed further without purification. Reduction of **26** with lithium aluminum hydride in THF gave rise to the two diastereomeric alcohols **27** and **28** in 15% and 75% yield, respectively. Treatment of amino acid **26** with acetic acid under reflux (conditions known to effect epimerization to the thermodynamically more stable diastereomer)^[17c] prior to reduction gave diastereomeric alcohols **27** and **28** in 45% and 15%, respectively. Alcohol **27** is a known precursor of (±)-thalictricavine to which it can be converted in two steps. Application of the known sequence^[17e] to **28** enabled the synthesis of (±)-epi-thalictricavine in 65% yield over two steps.

In summary, we have introduced a new type of intramolecular redox-Mannich reaction that is complementary to the classic Reinhoudt reaction in that it provides regioisomeric products differing only in the position of one methylene bridge.^[19] This transformation enables rapid access to products containing the tetrahydropyprotoberberine core. Further developments of the general concept are underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support from the NIH–NIGMS (R01GM101389) is gratefully acknowledged. We thank Dr. Tom Emge (Rutgers University) for crystallographic analysis.

References

1. a) Verboom W, Reinhoudt DN, Visser R, Harkema S. J. Org. Chem. 1984; 49:269. b) Verboom W, Hamzink MRJ, Reinhoudt DN, Visser R. Tetrahedron Lett. 1984; 25:4309. c) Nijhuis WHN, Verboom W, Reinhoudt DN, Harkema S. J. Am. Chem. Soc. 1987; 109:3136. d) Nijhuis WHN, Verboom W, Abu El-Fadl A, Harkema S, Reinhoudt DN. J. Org. Chem. 1989; 54:199.
2. Selected recent reviews: Matyus P, Elias O, Tapolcsanyi P, Polonka-Balint A, Halasz-Dajka B. Synthesis. 2006:2625. Platonova AY, Glukhareva TV, Zimovets OA, Morzherin YY. Chem.

Heterocycl. Compd. 2013; 49:357. Peng B, Maulide N. Chem. Eur. J. 2013; 19:13274. [PubMed: 24027042] Haibach MC, Seidel D. Angew. Chem. Int. Ed. 2014; 53:5010. Wang L, Xiao J. Adv. Synth. Catal. 2014; 356:1137.

3.

Selected recent examples of C–H bond functionalization via hydride-transfer: Barluenga J, Fananas-Mastral M, Aznar F, Valdes C. Angew. Chem. Int. Ed. 2008; 47:6594. Polonka-Balint A, Saraceno C, Ludányi K, Bényei A, Matyus P. Synlett. 2008:2846. Mori K, Ohshima Y, Ehara K, Akiyama T. Chem. Lett. 2009; 38:524. Murarka S, Zhang C, Konieczynska MD, Seidel D. Org. Lett. 2009; 11:129. [PubMed: 19067554] Zhang C, Murarka S, Seidel D. J. Org. Chem. 2009; 74:419. [PubMed: 19053590] McQuaid KM, Long JZ, Sames D. Org. Lett. 2009; 11:2972. [PubMed: 19548698] McQuaid KM, Sames D. J. Am. Chem. Soc. 2009; 131:402. [PubMed: 19099474] Ruble JC, Hurd AR, Johnson TA, Sherry DA, Barbachyn MR, Toogood PL, Bundy GL, Graber DR, Kamilar GM. J. Am. Chem. Soc. 2009; 131:3991. [PubMed: 19260642] Murarka S, Deb I, Zhang C, Seidel D. J. Am. Chem. Soc. 2009; 131:13226. [PubMed: 19711900] Vadola PA, Sames D. J. Am. Chem. Soc. 2009; 131:16525. [PubMed: 19852462] Dunkel P, Turos G, Benyei A, Ludanyi K, Matyus P. Tetrahedron. 2010; 66:2331. Zhou G, Zhang J. Chem. Commun. 2010; 46:6593. Kang YK, Kim SM, Kim DY. J. Am. Chem. Soc. 2010; 132:11847. [PubMed: 20701277] Zhou G, Liu F, Zhang J. Chem. Eur. J. 2011; 17:3101. [PubMed: 21328507] Haibach MC, Deb I, De CK, Seidel D. J. Am. Chem. Soc. 2011; 133:2100. [PubMed: 21280625] Mori K, Ehara K, Kurihara K, Akiyama T. J. Am. Chem. Soc. 2011; 133:6166. [PubMed: 21466211] Cao W, Liu X, Wang W, Lin L, Feng X. Org. Lett. 2011; 13:600. [PubMed: 21218793] He Y-P, Du Y-L, Luo S-W, Gong L-Z. Tetrahedron Lett. 2011; 52:7064. Jurberg ID, Peng B, Woestefeld E, Wasserloos M, Maulide N. Angew. Chem., Int. Ed. 2012; 51:1950. Chen L, Zhang L, Lv J, Cheng J-P, Luo S. Chem. Eur. J. 2012; 18:8891. [PubMed: 22706891] Sugiishi T, Nakamura H. J. Am. Chem. Soc. 2012; 134:2504. [PubMed: 22283631] Vadola PA, Carrera I, Sames D. J. Org. Chem. 2012; 77:6689. [PubMed: 22672002] Han Y-Y, Han W-Y, Hou X, Zhang X-M, Yuan W-C. Org. Lett. 2012; 14:4054. [PubMed: 22860987] He Y-P, Wu H, Chen D-F, Yu J, Gong L-Z. Chem. Eur. J. 2013; 19:5232. [PubMed: 23512426] Kang YK, Kim DY. Chem. Commun. 2014; 50:222. Mori K, Kurihara K, Akiyama T. Chem. Commun. 2014; 50:3729. Mori K, Kurihara K, Yabe S, Yamanaka M, Akiyama T. J. Am. Chem. Soc. 2014; 136:3744. [PubMed: 24564435] Cao W, Liu X, Guo J, Lin L, Feng X. Chem. Eur. J. 2015; 21:1632. [PubMed: 25421053] Wang P-F, Jiang C-H, Wen X, Xu Q-L, Sun H. J. Org. Chem. 2015; 80:1155. [PubMed: 25543720]

4.

Selected reviews on other types of redox-neutral transformations: Burns NZ, Baran PS, Hoffmann RW. Angew. Chem. Int. Ed. 2009; 48:2854. Mahatthananchai J, Bode JW. Acc. Chem. Res. 2014; 47:696. [PubMed: 24410291] Ketcham JM, Shin I, Montgomery TP, Krische MJ. Angew. Chem. Int. Ed. 2014; 53:9142. Huang H, Ji X, Wu W, Jiang H. Chem. Soc. Rev. 2015; 44:1155. [PubMed: 25417560]

5.

Selected reviews on amine C–H functionalization: Murahashi S-I. Angew. Chem., Int. Ed. Engl. 1995; 34:2443. Campos KR. Chem. Soc. Rev. 2007; 36:1069. [PubMed: 17576475] Murahashi S-I, Zhang D. Chem. Soc. Rev. 2008; 37:1490. [PubMed: 18648675] Li C-J. Acc. Chem. Res. 2009; 42:335. [PubMed: 19220064] Jazsar R, Hitce J, Renaudat A, Sofack-Kreutzer J, Baudoin O. Chem. Eur. J. 2010; 16:2654. [PubMed: 20143359] Yeung CS, Dong VM. Chem. Rev. 2011; 111:1215. [PubMed: 21391561] Pan SC. Beilstein J. Org. Chem. 2012; 8:1374. [PubMed: 23019474] Mitchell EA,

Peschiulli A, Lefevre N, Meerpoel L, Maes BUW. Chem. Eur. J. 2012; 18:10092. [PubMed: 22829434] Zhang C, Tang C, Jiao N. Chem. Soc. Rev. 2012; 41:3464. [PubMed: 22349590] Jones KM, Klusmann M. Synlett. 2012; 23:159. Prier CK, Rankic DA, MacMillan DWC. Chem. Rev. 2013; 113:5322. [PubMed: 23509883] Girard SA, Knauber T, Li C-J. Angew. Chem. Int. Ed. 2014; 53:74. Vo C-VT, Bode JW. J. Org. Chem. 2014; 79:2809. [PubMed: 24617516] Qin Y, Lv J, Luo S. Tetrahedron Lett. 2014; 55:551. Beatty JW, Stephenson CRJ. Acc. Chem. Res. 2015; 48:1474. [PubMed: 25951291]

6.

Seidel D. Acc. Chem. Res. 2015; 48:317. [PubMed: 25560649] Examples: Zhang C, De CK, Mal R, Seidel D. J. Am. Chem. Soc. 2008; 130:416. [PubMed: 18081292] Zhang C, Das D, Seidel D. Chem. Sci. 2011; 2:233. Deb I, Das D, Seidel D. Org. Lett. 2011; 13:812. [PubMed: 21247142] Ma L, Chen W, Seidel D. J. Am. Chem. Soc. 2012; 134:15305. [PubMed: 22963652] Das D, Sun AX, Seidel D. Angew. Chem. Int. Ed. 2013; 52:3765. Das D, Seidel D. Org. Lett. 2013; 15:4358. [PubMed: 23957378] Dieckmann A, Richers MT, Platonova AY, Zhang C, Seidel D, Houk KN. J. Org. Chem. 2013; 78:4132. [PubMed: 23517448] Chen W, Wilde RG, Seidel D. Org. Lett. 2014; 16:730. [PubMed: 24328366] Richers MT, Breugst M, Platonova AY, Ullrich A, Dieckmann A, Houk KN, Seidel D. J. Am. Chem. Soc. 2014; 136:6123. [PubMed: 24689802] Chen W, Seidel D. Org. Lett. 2014; 16:3158. [PubMed: 24857691] Jarvis CL, Richers MT, Breugst M, Houk KN, Seidel D. Org. Lett. 2014; 16:3556. [PubMed: 24927364]

7.

Selected reviews on azomethine ylide chemistry: Padwa A, Pearson WH. Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products. 2002; 59 Chichester, U. K. Wiley Coldham I, Hufton R. Chem. Rev. 2005; 105:2765. [PubMed: 16011324] Pandey G, Banerjee P, Gadre SR. Chem. Rev. 2006; 106:4484. [PubMed: 17091927] Pinho e Melo TMVD. Eur. J. Org. Chem. 2006:2873. Najera C, Sansano JM. Top. Heterocycl. Chem. 2008; 12:117. Stanley LM, Sibi MP. Chem. Rev. 2008; 108:2887. [PubMed: 18613728] Nyerges M, Toth J, Groundwater PW. Synlett. 2008:1269. Burrell AJM, Coldham I. Curr. Org. Synth. 2010; 7:312. Anac O, Gungor FS. Tetrahedron. 2010; 66:5931.

8.

Related studies by others, examples: Zheng L, Yang F, Dang Q, Bai X. Org. Lett. 2008; 10:889. [PubMed: 18260668] Zheng Q-H, Meng W, Jiang G-J, Yu Z-X. Org. Lett. 2013; 15:5928. [PubMed: 24237286] Lin W, Cao T, Fan W, Han Y, Kuang J, Luo H, Miao B, Tang X, Yu Q, Yuan W, Zhang J, Zhu C, Ma S. Angew. Chem. Int. Ed. 2014; 53:277. Haldar S, Mahato S, Jana CK. Asian J. Org. Chem. 2014; 3:44. Rahman M, Bagdi AK, Mishra S, Hajra A. Chem. Commun. 2014; 50:2951. Li J, Wang H, Sun J, Yang Y, Liu L. Org. Biomol. Chem. 2014; 12:2523. [PubMed: 24619486]

9. Chen W, Kang Y, Wilde RG, Seidel D. Angew. Chem. Int. Ed. 2014; 53:5179.

10. a) Chrzanowska M, Rozwadowska MD. Chem. Rev. 2004; 104:3341. [PubMed: 15250744] b) Grycova L, Dostal J, Marek R. Phytochemistry. 2007; 68:150. [PubMed: 17109902] c) Gonzalez-Lopez M, Shaw JT. Chem. Rev. 2009; 109:164. [PubMed: 19140773] d) Bhadra K, Kumar GS. Med. Res. Rev. 2011; 31:821. [PubMed: 20077560]

11. Liu P, Tao K, Zhao L, Shen W, Zhang J. Tetrahedron Lett. 2012; 53:560.

12.

Dealkoxycarbonylation product **6** was found to be relatively unstable under the reaction conditions.

13.

Interestingly, an acid promoter was not strictly required for the reaction of THIQ with **3a**. Without acid at 90 °C under otherwise optimal conditions, product **9a** was isolated in 70% yield after eight hours.

14.

Leading references on malonate dealkoxycarbonylation: Krapcho AP. ARKIVOC. 2007; (ii):1. Krapcho AP, Ciganek E. Organic Reactions. 2013; 81:1.

15.

Tertiary amines appear to be ineffective promoters. For instance, *N*-methyl pyrrolidine failed to promote the dealkoxycarbonylation of **3a** under a variety of conditions.

16. Manske RHF. J. Am. Chem. Soc. 1953; 75:4928.

17.

Selected syntheses of thalictricavine and related compounds: Kaneko H, Naruto S. J. Org. Chem. 1969; 34:2803. Yu C-K, MacLean DB, Rodrigo RGA, Manske RHF. Can. J. Chem. 1970; 48:3673. Cushman M, Gentry J, Dekow FW. J. Org. Chem. 1977; 42:1111. [PubMed: 845705] Dean RT, Rapoport H. J. Org. Chem. 1978; 43:4183. Cushman M, Dekow FW. J. Org. Chem. 1979; 44:407. Iwasa K, Cushman M. Heterocycles. 1981; 16:901. Iwasa K, Gupta YP, Cushman M. J. Org. Chem. 1981; 46:4744. Iwasa K, Gupta YP, Cushman M. Tetrahedron Lett. 1981; 22:2333. Hanaoka M, Yoshida S, Mukai C. J. Chem. Soc.-Chem. Commun. 1985:1257. Iwasa K, Kamigauchi M, Ueki M, Taniguchi M. Eur. J. Med. Chem. 1996; 31:469. Matulenko MA, Meyers AI. J. Org. Chem. 1996; 61:573. [PubMed: 11666977] Hanaoka M, Hirasawa T, Cho WJ, Yasuda S. Chem. Pharm. Bull. 2000; 48:399. [PubMed: 10726865] Orito K, Satoh Y, Nishizawa H, Harada R, Tokuda M. Org. Lett. 2000; 2:2535. [PubMed: 10956540] Suau R, Najera F, Rico R. Tetrahedron. 2000; 56:9713. Boudou M, Enders D. J. Org. Chem. 2005; 70:9486. [PubMed: 16268624] Cheng J-J, Yang Y-S. J. Org. Chem. 2009; 74:9225. [PubMed: 19950885] Resch V, Lechner H, Schrittwieser JH, Wallner S, Gruber K, Macheroux P, Kroutil W. Chem. Eur. J. 2012; 18:13173. [PubMed: 22962029] Mori K, Kawasaki T, Akiyama T. Org. Lett. 2012; 14:1436. [PubMed: 22390141] Pouilhes A, Baltaze JP, Kouklovsky C. Synlett. 2013; 24:1805. Gatland AE, Pilgrim BS, Procopiou PA, Donohoe TJ. Angew. Chem. Int. Ed. 2014; 53:14555.

18.

See the Supporting Information for details.

19.

For a complementary approach that provides related products in a different oxidation state (based on imines and *o*-malonate-benzoic acids) see: Unsworth WP, Kitsiou C, Taylor RJK. Org. Lett. 2013; 15:258. [PubMed: 23265307]

Reinhoudt reaction: **This work:** **Selected tetrahydroprotoberberine alkaloids:**

Scheme 1.
Reinhoudt vs. Redox-Mannich Reactions.

Scheme 2.

Scope of the Intramolecular Redox-Mannich Reaction with Pyrrolidine.

9a, 83% (3 h)

9b, 78% (7 h)

9c, 76% (9 h)

9d, 85% (24 h)

9e, 50% (24 h)

9f, 43% (10 min)
@ 150 °C (μW)

Scheme 3.
Intramolecular Redox-Mannich Reaction with THIQ and Related Amines.

Scheme 4.
Pyrrolidine β -functionalization.

Scheme 6.
Mechanistic considerations.

Scheme 7.
Synthetic Applications.

Table 1

Evaluation of Reaction Conditions.^[a]

entry	additive (equiv)	Temp [°C]	time	yield 5a (%)	yield 7 (%)	yield 6 (%)
1	-	reflux	12 h	5	-	8
2	AcOH (0.2)	reflux	4 h	39	-	-
3	AcOH (1)	reflux	1 h	53	18	-
4	AcOH (5)	reflux	1.5 h	54	8	-
5	AcOH (10)	reflux	3 h	68	15	-
6	2-EHA (10)	reflux	1.5 h	76	trace	-
7	2-EHA (5)	reflux	2 h	74	trace	-
8	PhCO ₂ H (10)	reflux	3 h	52	10	12
9	pivalic acid (10)	reflux	1 h	71	15	-
10	2-EHA (10)	130 (μW)	45 min	57	trace	10
11	2-EHA (10)	150 (μW)	10 min	72	trace	trace

^[a] All reactions were performed on a 0.25 mmol scale and were terminated upon the disappearance of **3a** as judged by TLC analysis.