A Rapid Synthesis of 2-Aryl Polyhydroxylated Pyrrolidines

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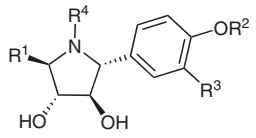
Received 7 April 2010

Abstract: Friedel–Crafts-type reaction of electron-rich aromatic compounds with polyhydroxylated cyclic nitrones catalyzed by Brønsted acid afforded 2-aryl polyhydroxylated pyrrolidines in good to excellent yields with high diastereoselectivity under mild conditions.

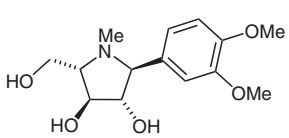
Key words: 2-aryl polyhydroxylated pyrrolidines, iminosugars, Brønsted acid, polyhydroxylated cyclic nitrones, Friedel–Crafts reaction

Iminosugars (polyhydroxylated alkaloids) have attracted considerable attention for their remarkable biological activities and potential as pharmaceuticals.[1] Polyhydroxylated pyrrolidines carrying an aromatic substituent on the iminosugar ring, that is, 2-aryl polyhydroxylated pyrrolidines, are a rare class of alkaloids found in nature (Figure 1).[2] Due to their intriguing molecular structures and important biological activities, many efforts have been made in developing synthetic methods for these alkaloids.[3]

The synthesis and biological evaluation of 2-aryl polyhydroxylated pyrrolidines have hence become an area of interest, and a number of derivatives had been synthesized for the purpose of searching for new biologically active molecules.[4]



(–)-codonopsinine (**1**) R^1 = Me, R^2 = R^4 = Me, R^3 = H
(–)-codonopsine (**2**) R^1 = Me, R^2 = R^4 = Me, R^3 = OMe
radicamine A (**3**) R^1 = CH_2OH, R^2 = Me, R^3 = OH, R^4 = H
radicamine B (**4**) R^1 = CH_2OH, R^2 = R^3 = R^4 = H



codonopsinol (**5**)

Figure 1 Examples of 2-aryl polyhydroxylated pyrrolidines

SYNLETT 2010, No. 11, pp 1609–1616
Advanced online publication: 11.06.2010
DOI: 10.1055/s-0029-1258085; Art ID: W05310ST

Though many elegant synthetic procedures have already been developed for the synthesis of 2-aryl iminosugars, there still lacks of efficient methods for the rapid generation of 2-aryl iminosugars with structural diversities which is essential for in-depth structure–activity study. In this context, we decided to examine the direct arylation of polyhydroxylated cyclic nitrones via the Friedel–Crafts-type reactions which, we envisage, might provide an efficient method for the synthesis of compound libraries of 2-aryl iminosugars, because polyhydroxylated cyclic nitrones have recently emerged as potentially powerful synthons for iminosugars synthesis.[5]

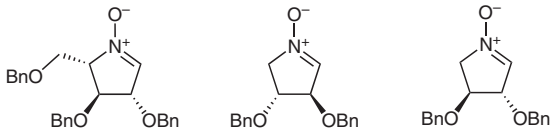


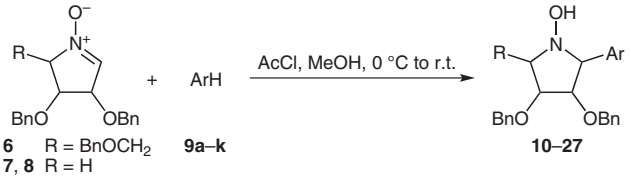
Figure 2 Polyhydroxylated cyclic nitrones

While the greatest interest associated with nitrones has been focused on the study of 1,3-dipolar cycloaddition reactions,[6] numerous reactions with nucleophiles[7] also merit attention. Apart from organometallics, electron-rich aromatic compounds could also be used in the reactions with nitrones. The Friedel–Crafts alkylation of nitrones was first reported by Banerji in 1982,[8] and further explored by Vallée and others.[9] In view of their exquisite and special chemical reactivity and stereochemistry in comparison with those of other usual nitrones, an exploratory study on the Friedel–Crafts reaction of polyhydroxylated cyclic nitrones with electron-rich aromatic compounds would be of significance for developing a new synthetic method of 2-aryl iminosugars, as well as for a better understanding of the nitrone chemistry.

O-Benzyl-protected polyhydroxylated cyclic nitrones **6**–**8**, which were prepared following the reported procedures (Figure 2),[10] were chosen for the investigation. In our initial study, indole **9a** was employed in the model reaction with cyclic nitrones, not only because it is fairly electron rich, but also because the indole nucleus has been found in myriad alkaloids and biologically active heterocycles.[11] Thus, the reaction of indole with nitrone **6** was performed in methanol at ambient temperature in the presence of

HCl, which was generated by addition of acetyl chloride to methanol (10% v/v) at 0 °C. As anticipated, the desired 2-(1*H*-indol-3-yl)-pyrrolidine **10** was formed in good yield (84%) and moderate diastereoselectivity (*trans*/*cis* or dr = 80:20, determined by ^{1}H NMR of crude mixture of products) in 4 hours.

Table 1 Reaction of Electron-Rich Aromatics with Cyclic Nitrones



6 R = $BnOCH_2$ **7**, **8** R = H **9a–k** **10–27**

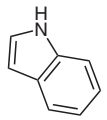
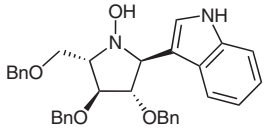
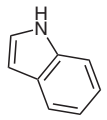
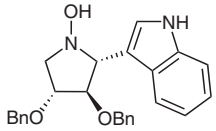
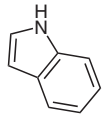
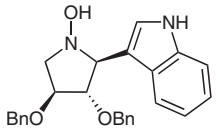
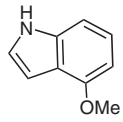
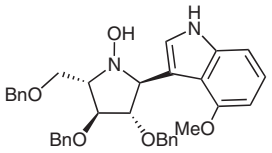
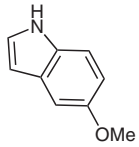
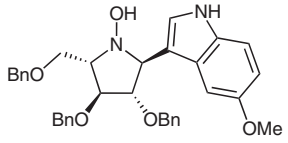
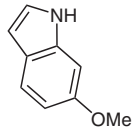
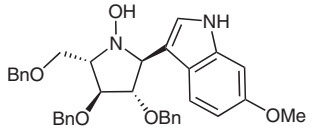
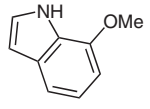
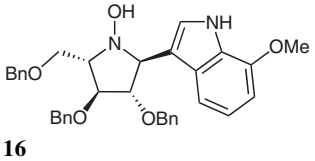
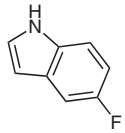
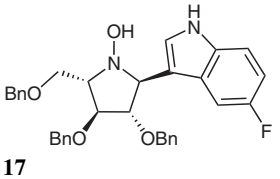
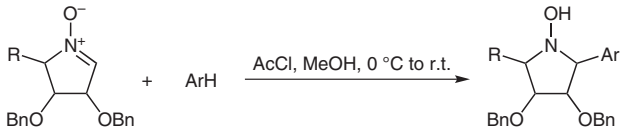
Entry	Nitrone	ArH	Time (h)	Major product	Yield (%)[a] (dr[b])
1	**6**	 **9a**	4	 **10**	96 (98:2)
2	**7**	 **9a**	4	 **11**	97 (95:5)
3	**8**	 **9a**	4	 **12**	93 (95:5)
4	**6**	 **9b**	4	 **13**	93 (99:1)
5	**6**	 **9c**	4	 **14**	93 (95:5)
6	**6**	 **9d**	4	 **15**	95 (98:2)
7	**6**	 **9e**	4	 **16**	95 (97:3)
8	**6**	 **9f**	8	 **17**	91 (92:8)

Table 1 Reaction of Electron-Rich Aromatics with Cyclic Nitrones (continued)



6 R = $BnOCH_2$ **7**, **8** R = H **9a–k** **10–27**

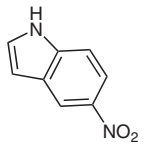
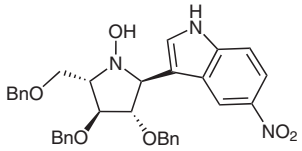
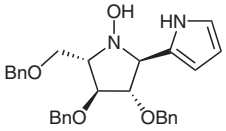
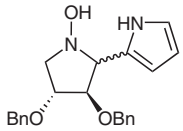
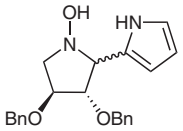
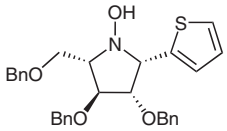
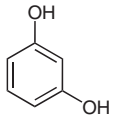
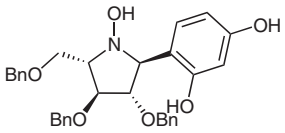
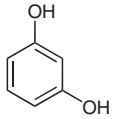
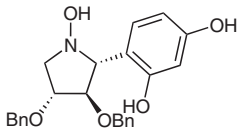
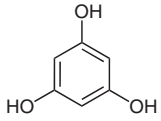
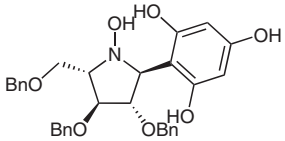
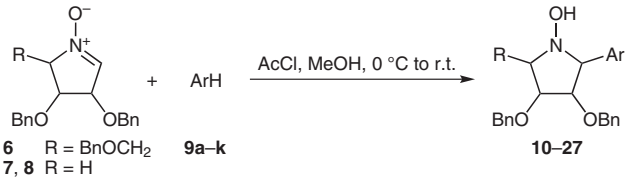
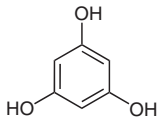
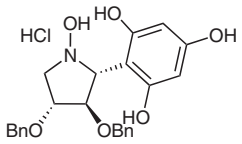
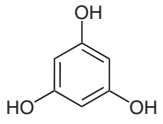
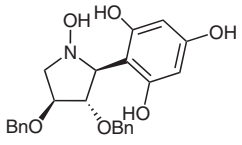
Entry	Nitrone	ArH	Time (h)	Major product	Yield (%)[a] (dr[b])
9	**6**	 **9g**	72	 **18**	81 (92:8)
10	**6**	 **9h**	8	 **19a**	91 (87:13)
11	**7**	 **9h**	12	 **20a–b**	88[c] (73:27)
12	**8**	 **9h**	12	 **21a–b**	89[c] (73:27)
13	**6**	 **9i**	168	 **22a**	73[d] (57:43)
14	**6**	 **9j**	8	 **23**	93 (99:1)
15	**7**	 **9j**	12	 **24**	84 (93:7)
16	**6**	 **9k**	12	 **25**	84[e] (99:1)

Table 1 Reaction of Electron-Rich Aromatics with Cyclic Nitrones (continued)



6 R = $BnOCH_2$ **7**, **8** R = H **9a–k** **10–27**

Entry	Nitrone	ArH	Time (h)	Major product	Yield (%)[a] (dr[b])
17	**7**	 **9k**	12	 **26**	88[e] (99:1)
18	**8**	 **9k**	12	 **27**	81[e] (99:1)

[a] Isolated overall yield.
[b] Determined by ^{1}H NMR.
[c] Inseparable mixture.
[d] Reaction conditions: AcCl (2 equiv), MeOH (5mL), 0 °C to r.t.
[e] In diluted solvent, 0 °C.

When the reaction was conducted in the presence of the reduced amount of HCl, that is, addition of AcCl (0.5% v/v) to the reaction solution, while maintaining the reaction temperature first at 0 °C then slowly warmed to room temperature in an argon atmosphere, the reaction afforded the *trans* isomer of the hydroxylamine **10** in 96% isolated yield with high diastereoselectivity (dr = 98:2; Table 1, entry 1).

The scope and limitation of this reaction were then examined. It was found that a variety of electron-rich aromatics underwent this Friedel–Crafts-type reaction smoothly, producing the desired products in good to excellent yields with high diastereoselectivity (Table 1). Various indole derivatives **9b–g** worked well and exhibited high diastereoselectivity (>92:8; Table 1, entries 1–9), although 5-fluoro-indole **9f** and 5-nitro-indole **9g**, with electron-withdrawing groups, required longer reaction time for full conversion (Table 1, entry 8 and 9). However, despite moderate to high reaction yields, both pyrrole and thiophene displayed moderate diastereoselectivity (Table 1, entries 10 or 13; dr 87:13 for pyrrole, 57:43 for thiophene, determined by ^{1}H NMR).

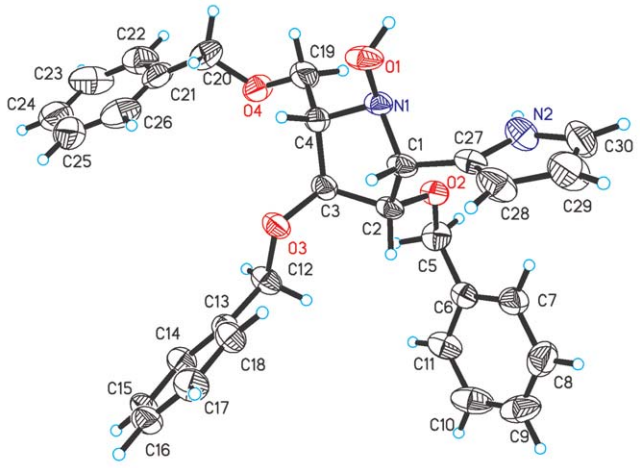


Figure 3 X-ray structure of **19b**

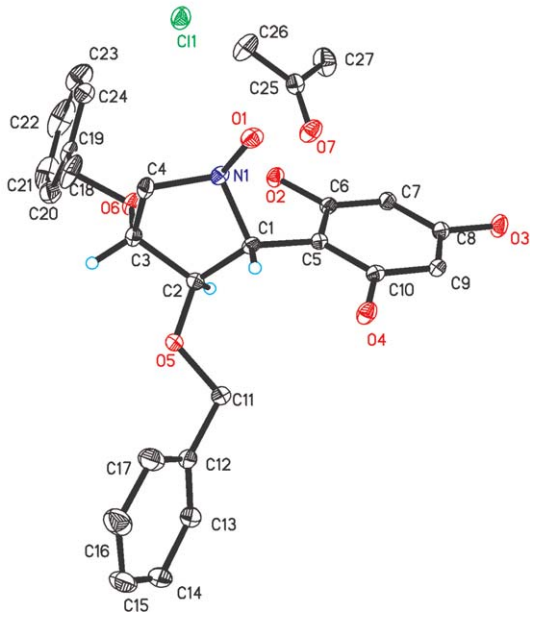


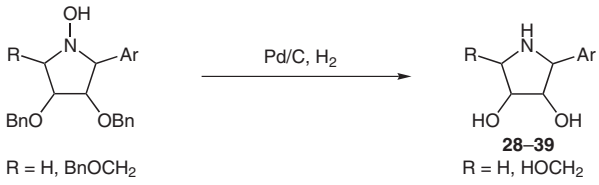
Figure 4 X-ray structure of **26**, partial H atoms bonded to C atoms have been omitted for clarity

Attempts to apply this method in the synthesis of natural products codonopsinol (**3**) and radicamines A (**4**) failed due to the relatively poor nucleophilicity of the 1,2-dimethoxybenzene and guaiacol. However, both resorcinol (**9j**) and phloroglucinol (**9k**) were good substrates for the reaction, resulting in the corresponding hydroxylamines **23** and **25** in excellent yield and with high diastereoselectivity (Table 1, entry 14 and 16). All the structures of the products **10**–**27** were determined by NMR (^{1}H NMR, ^{13}C NMR, and NOE measurements), IR, MS, and the structures of the hydroxylamines **19b** (Table 1, the minor isomer of entry 10) and **26** were further confirmed by X-ray crystal structures. (Figure 3, Figure 4).[12]

Reactivities of the cyclic nitrones **7** and **8** were found to be similar to that of cyclic nitrone **6**. For example, good to excellent yields and high diastereoselectivity (dr >93:7) were achieved in the reactions of indole **9a** or resorcinol **9j** with **7** or **8** (Table 1, entries 2, 3, 15). Once again, the reaction of pyrrole **9h** with either **7** or **8** resulted in good yields but poor diastereoselectivity (Table 1, entries 11 and 12: dr = 73:27, determined by ^{1}H NMR).

Catalytic hydrogenation of some of the *O*-benzyl cyclic hydroxyamines **10**–**27** afforded the deprotected 2-aryl pyrrolidines **28**–**39**. The use of the Pd/C–AcOH system for the debenzylation resulted in efficient benzyl group hydrogenolysis while avoided reduction of the aromatic heterocycles at the same time (Table 2, entries 1–6, 8). As was expected, the hydrogenation of the relatively more complicated substrate, 5-nitroindole derivate **18**, resulted in a complex mixture of products (Table 2, entry 7).

Table 2 Debenzylation of *N*-Hydroxypyrrolidines



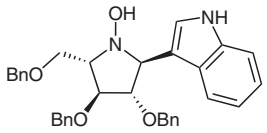
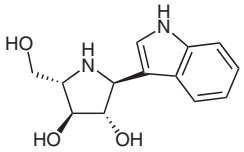
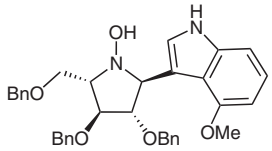
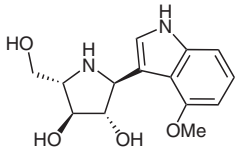
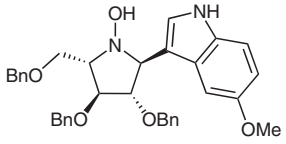
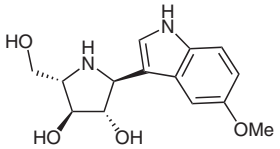
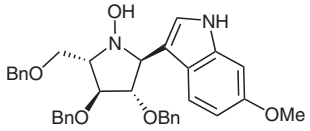
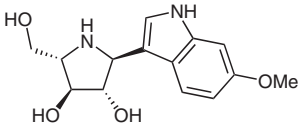
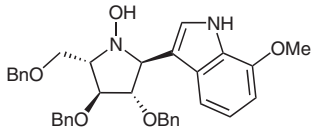
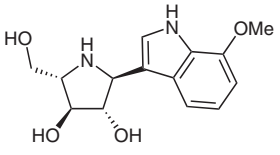
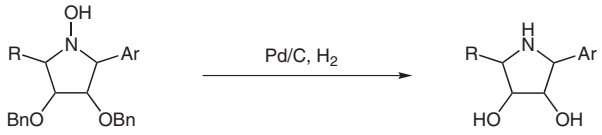
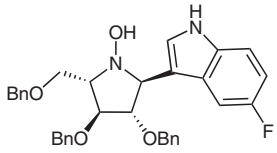
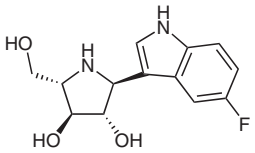
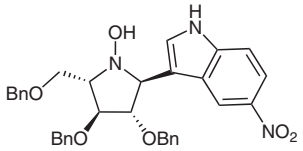
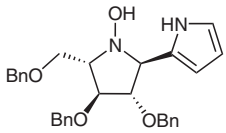
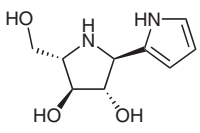
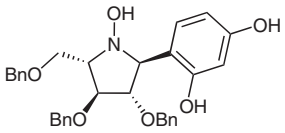
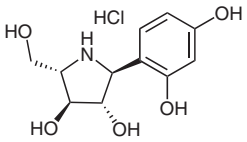
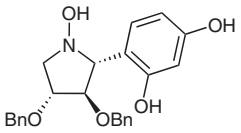
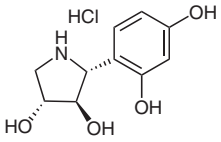
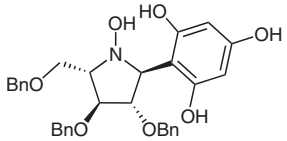
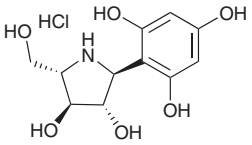
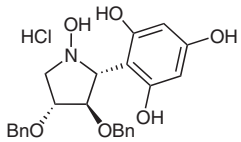
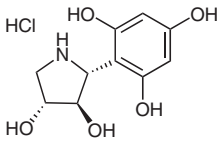
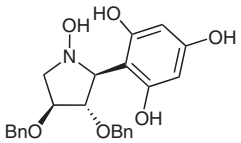
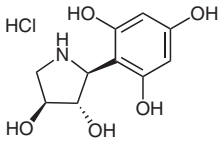
Entry	Reactant	Product	Isolated yield (%)
1	 **10**	 **28**	85[a]
2	 **13**	 **29**	80[a]
3	 **14**	 **30**	82[a]
4	 **15**	 **31**	79[a]
5	 **16**	 **32**	81[a]

Table 2 Debenzylation of *N*-Hydroxypyrrolidines (continued)

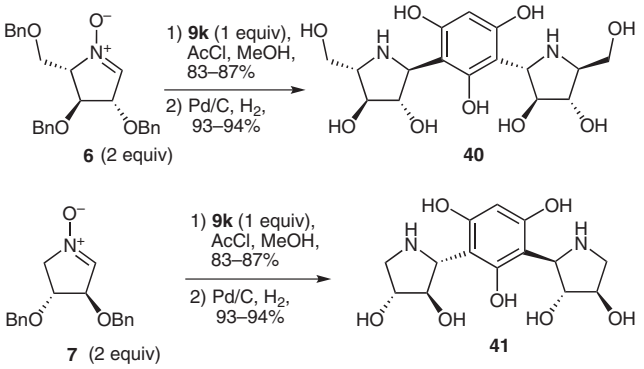


R = H, $BnOCH_2$ **28–39** R = H, $HOCH_2$

Entry	Reactant	Product	Isolated yield (%)
6	 **17**	 **33**	79[a]
7	 **19a**	–	0[a]
8	 **19a**	 **34**	77[a]
9	 **23**	 **35**	95[b]
10	 **24**	 **36**	96[b]
11	 **25**	 **37**	92[b]
12	 **26**	 **38**	97[b]
13	 **27**	 **39**	93[b]

[a] Reagents and conditions: Pd/C 20%, AcOH, 35 °C.
[b] Reagents and conditions: Pd/C 10%, MeOH, r.t.

Finally, it is worth mentioning that treatment of highly active phloroglucinol **9k** with nitrones **6–8** in diluted reaction solution at 0 °C afforded [1+1] adducts as major products (dr = 99:1, Table 1, entries 16–18). Treatment of 1 equivalent of phloroglucinol **9k** with 2 equivalents of nitrone resulted in the formation of [1+2] adducts, that is, the 2,4-disubstituted phloroglucinols **40** and **41** as the major products, with only a trace amount of the corresponding [1+3] adducts being detected (Scheme 1).



Scheme 1 The synthesis of 2,4-disubstituted phloroglucinols

In summary, the Brønsted acid promoted F–C reaction of polyhydroxylated cyclic nitrones with electron-rich aromatic compounds is an efficient method for the rapid synthesis of the 2-aryl iminosugars. The method is capable of diversity-oriented synthesis of compound library of 2-aryl iminosugars, which is essential for the structure–activity study of this special class of iminosugars.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

This work is supported by The National Natural Science Foundation of China (No. 20672117), The National Basic Research Program of China (No. 2009CB526511), The Ministry of Science and Technology and the Ministry of Health of the P. R. of China (No. 2009ZX09501-006), and The Chinese Academy of Sciences.

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(12) The crystal structures of **19b** and **26** have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition numbers CCDC 756237 and 756238, respectively.