Coupling Reactions

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Palladium-Catalyzed Coupling Reactions of Thioimidate N-Oxides: Access to α-Alkenyl- and α-Aryl-Functionalized Cyclic Nitrones**

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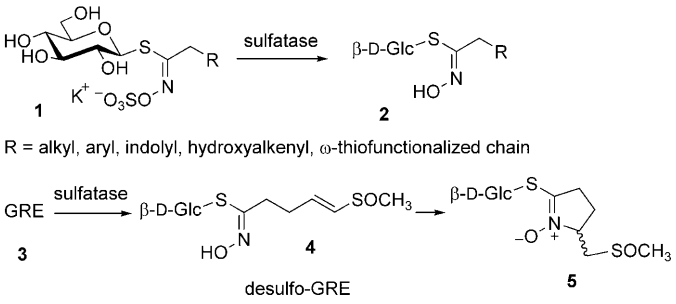
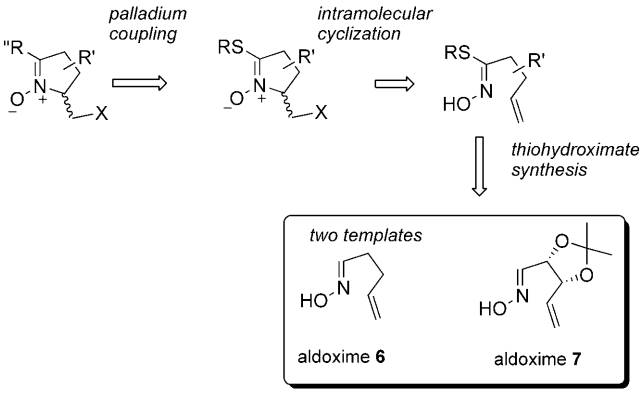
Cyclic nitrones have recently emerged as highly targeted molecules for their diversity and/or potential as therapeutic compounds,[1] spin-trapping agents,[2] and for their participation in numerous chemical transformations.[3] Cyclic nitrones have mainly been used in synthetic approaches towards natural products and biologically active compounds.[4] In those multistep syntheses the most recent methods involved carbohydrate templates.[5] The usefulness of cyclic nitrones for developing bioactive compounds is based on the broad reactivity of the imine N-oxide fragment, but the main drawback resides in the fact that nearly all methods lead to aldonitrones[3]—few methods lead to ketonitrones—with a limited range of substituents.[6] Together with our long-term study of sulfur-containing plant secondary metabolites,[7] the glucosinolate family has been the starting point for the development of an original method to generate alkenyl and aryl ketonitrones. Glucosinolates **1** are remarkable for their structural homogeneity: a hydrophilic β-D-glucopyrano framework bearing an O-sulfated anomeric (*Z*)-thiohydroximate moiety connected to a fairly hydrophobic aglycon side chain.[8] These metabolites are largely involved in human and animal nutrition and have made an impact on health issues.[9] This aspect has led to the development of European standard analytical procedures for determining the amount of glucosinolates in plants.[10] This HPLC analysis requires preliminary enzymatic desulfation to produce desulfoglucosinolates **2**, which are generally more stable (Scheme 1). Our research group has recently disclosed the unique and intriguing behavior of glucoraphenin (GRE) **3** and features conversion of its desulfated derivative **4** into an unprecedented cyclic thioimidate N-oxide **5**.[11] The desulfoglucoraphenin **4** spontaneously underwent intramolecular Michael addition of the thiohydroximate moiety onto the vinyl sulfoxide, and produced **5** in good yield.

The formation of a thioimidate N-oxide prompted us to design a general method for its preparation with a view to further exploring the chemical capability of this rarely known functional group.[12] Keeping in mind our previous explorations of the Liebeskind–Srogl reaction,[13] we considered applying the cross-coupling methodology to cyclic thioimidate N-oxides, aiming to give a modulated synthetic approach to ketonitrones.



Scheme 1. Desulfation of glucosinolates.

Despite the mediocre stability observed for the "α-alkylsulfanylnitrone" **5**, we have designed a closely related simplified thiohydroximate model,[14] bearing in place of the vinyl sulfoxide group a terminal double bond, which is able to undergo electrophilic activation. Formally speaking, our retrosynthetic approach (Scheme 2) is similar to those previously developed by Grigg et al.[15] and by Jäger and co-workers[6a] for the formation of nitrones from aldoximes.



Scheme 2. Retrosynthetic approach.

The first aldoxime template **6** was prepared according to the procedure of Jäger and co-workers.[6a] The corresponding thiohydroximate was synthesized by a standard two-step process involving α-chlorination of the oxime by N-chloro-

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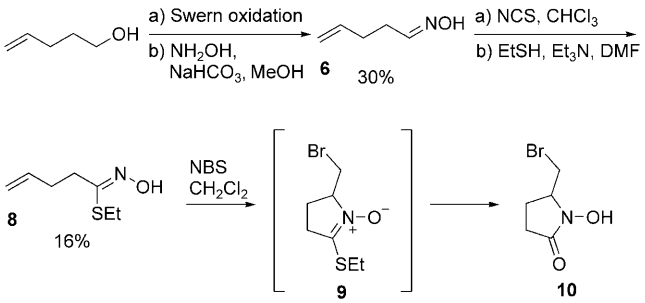
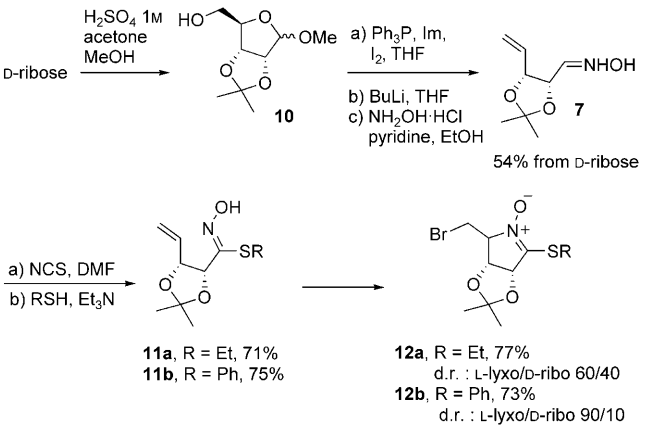
succinimide (NCS), then alkylsulfanyl insertion under basic reaction conditions. As expected, the reaction selectively afforded the *Z*-configured thiohydroximate **8**, albeit in rather poor yield (Scheme 3). Nonetheless, we attempted the halocyclization reaction which proved unsatisfactory: the resulting thioimidate N-oxide **9** quickly hydrolyzed during workup to produce the cyclic hydroxamic acid **10** in 56% yield.



Scheme 3. Tentative approach to a simplified model. DMF = *N*,*N*-dimethylformamide.

To build up a better stabilized alkylsulfanyl nitrone, we turned to a more structurally rigid precursor. By following a previously described procedure the second template, aldoxime **7**, was synthesized in four steps and in 54% overall yield from D-ribose (Scheme 4).[16] The thiohydroximate **11a** was

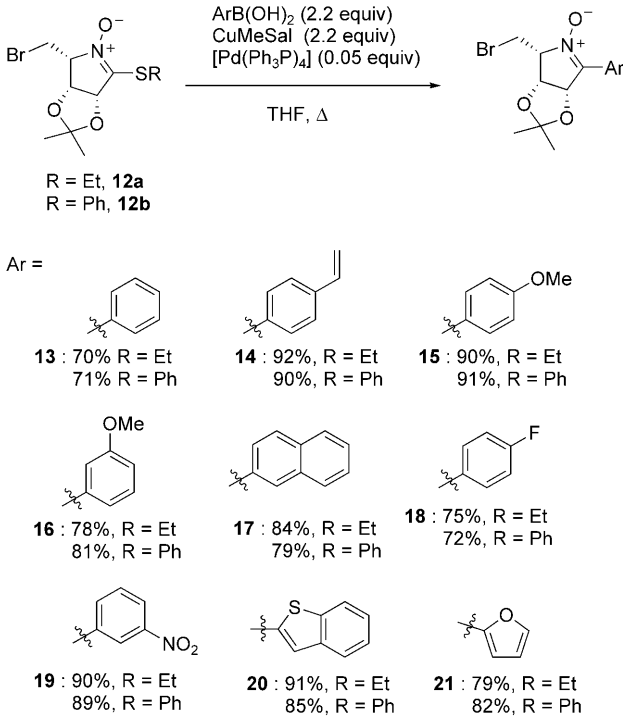


Scheme 4. Access to D-ribose-derived thioimidate N-oxides. THF = tetrahydrofuran.

subsequently obtained in 71% yield by using a slightly modified procedure.[7] Similarly, the phenylsulfanyl analogue **11b** could be obtained in 75% yield by treatment **7** with thiophenol. When subjected to halocyclization with *N*-bromosuccinimide (NBS), the thiohydroximates **11** were readily converted into the N-oxides **12a** and **12b** in 77% and 73% yield, respectively.[15b,16a] The stereoselectivities observed matched those reported for the halocyclization of aldoximes, with a preferred L-lyxo configuration of the cyclic nitrone **12**. The sulfanyl moiety greatly impacts the stereoselective outcome: a much higher 9:1 diastereomeric ratio was observed for the phenylsulfanyl derivative **12b** whereas the ethylsulfanyl derivative **12a** reached only 6:4 d.r.

Owing to the rigidity of the carbohydrate backbone, we therefore had in hand a stable thioimidate N-oxide template. In both cases, the major epimers could be separated from each other for further chemical studies. Both phenylsulfanyl and ethylsulfanyl moieties were considered as leaving groups in our investigation of the ability of the thioimidate N-oxides to interact efficiently with palladium to perform cross-coupling reactions under Liebeskind–Srogl conditions.[13]

The ethylsulfanyl derivative **12a** was first subjected to a Suzuki–Miyaura coupling reaction with phenylboronic acid, by following the procedure developed in our laboratory for benzylsulfanyl oxazolines,[17] and the phenylnitrone **13** was isolated in 70% yield. The phenylsulfanyl derivative **12b** reacted similarly and gave 71% yield of **13**. We subsequently engaged a diverse set of boronic acids in the cross-coupling reaction (Scheme 5).

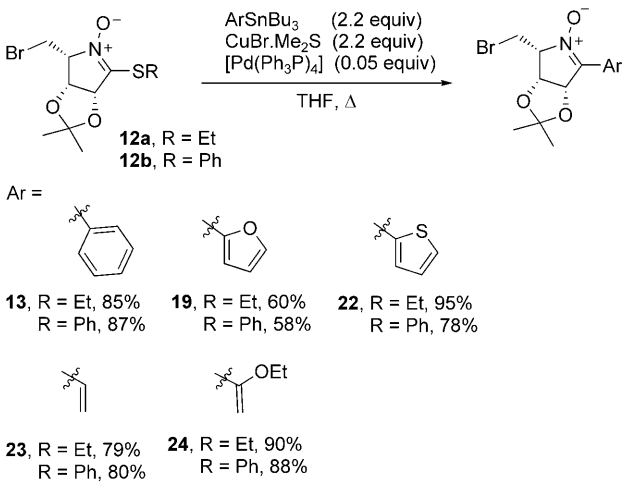


Scheme 5. Modified Suzuki coupling reaction.

With the ethylsulfanyl derivative **12a**, substituted phenyl reagents proved quite efficient in most cases—in particular with electron-donating groups—and afforded the corresponding ketonitrones **14** and **15** in 92% and 90% yields, respectively. Compared to the *para*-substituted derivative, the *meta*-methoxy derivative **16** proved slightly less effective. The β-naphthyl derivative **17** was also formed in good yield. The presence of an electron-withdrawing group did not significantly hamper the reaction, as shown from the 75% yield of *para*-fluorophenyl derivative **18** or from the 90% yield of *meta*-nitrophenyl derivative **19**. The efficacy of the phenylsulfanyl substrate **12b** in coupling reactions with the

substituted phenyl boronic acids was comparable, with yields ranging from 72% to 91%. When heteroaryl boronic acids such as benzothiophene- and furan-derived coupling reagents were engaged, the corresponding heteroaryl nitrones **20** and **21** were obtained from **12a** in 91% and 79% yields, respectively, or from **12b** in 85% and 82% yields, respectively. In contrast with those gratifying results, *ortho*-bromophenyl boronic acid proved less effective with yields around 60%. Furthermore, both 4-pyridyl boronic acid and its glycol ester appeared to be unsuccessful under these cross-coupling reaction conditions.

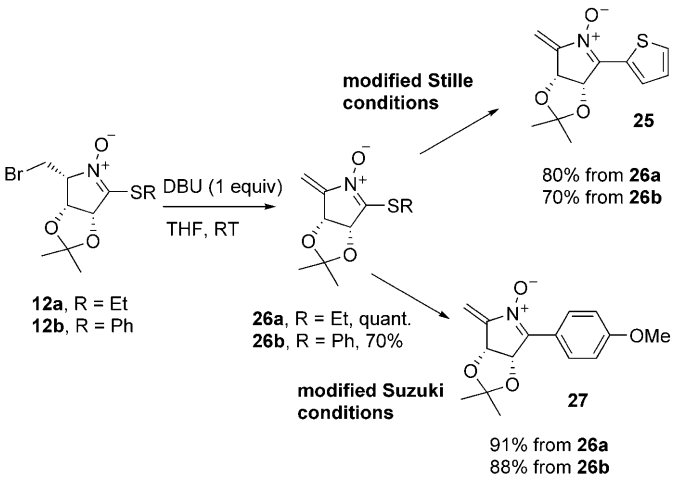
Our thioimidate N-oxide substrates were then subjected to the Stille cross-coupling reaction: the modified conditions used were the same as above except that CuMeSal was replaced by CuBr.Me_2S (Scheme 6). Similarly, treatment of



Scheme 6. Modified Stille coupling reaction.

tri-*n*-butylphenyl stannane with both **12a** and **12b** afforded the phenyl-substituted nitrone **13**, which were isolated in higher yields (85% and 87% yield, respectively) compared to when the Suzuki coupling was used. In contrast, 2-(tri-*n*-butylstannyl)furan proved less reactive, and the furyl nitrone **19** that was produced from either **12a** or **12b** was afforded in approximately 60% yield. The same protocol applied to 2-(tri-*n*-butylstannyl)thiophene afforded much better yields of the thienyl nitrone **22** from either **12a** or **12b** (95% and 78% yield, respectively). Finally, two vinyl stannyl reagents were also tested: in both cases, the coupling reaction smoothly afforded the corresponding nitrones **23** (ca. 80% yield from either **12a** or **12b**) and **24**, albeit purification was rather difficult and only a partially pure compound was obtained. When we took a closer look at the results obtained for the coupling reaction with 2-(tri-*n*-butylstannyl)thiophene, a side product **25** (Scheme 7) resulting from HBr elimination was detected and isolated in 5% yield when **12a** was used.

Our interest was spurred by the intriguing structure of **25** and therefore we explored an optimized pathway to prepare this unique *exo*-methylene nitrone functional system (Scheme 7). Deliberate HBr elimination in our thioimidate N-oxide substrates was more efficiently effected using DBU



Scheme 7. Reactivity of *exo*-methylene thioimidate N-oxide compounds. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

in THF: the *exo*-methylene thioimidate N-oxide **26a** was obtained in quantitative yield, and the phenyl analogue **26b** in 70% yield. Then our modified Suzuki and Stille reaction conditions were applied to both **26a** and **26b** in cross-coupling reactions. Under Stille conditions, the stannyl thiophene reagent afforded the *exo*-methylene thienyl nitrone **25** from either **26a** or **26b** (80% and 70% yield, respectively). Applying Suzuki conditions with *para*-methoxyphenyl boronic acid more efficiently led to the aryl nitrone **27** from either **26a** or **26b** (91% and 88% yield, respectively).

In summary, while exploring the synthesis and properties of the rarely studied thioimidate N-oxide functional group we have disclosed an original method to prepare aryl- and vinyl-substituted cyclic ketonitrones, from D-ribose-derived cyclic thioimidate N-oxides, a chiral template, by way of the Liebeskind–Srogl reaction. The scope of this novel synthetic approach to cyclic ketonitrones appears to be broad and efficient by using both modified Suzuki and Stille procedures. The intriguing *exo*-methylene thioimidate N-oxides **26a** and **26b** also gave good results in the coupling reactions. Further exploration on improved methods for the synthesis and investigation of the reactivity features of the unique thioimidate N-oxide functional group are currently being investigated in our laboratory.

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