Heterocycles

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Generation of an 4-Isoxazolyl Anion Species: Facile Access to Multifunctionalized Isoxazoles

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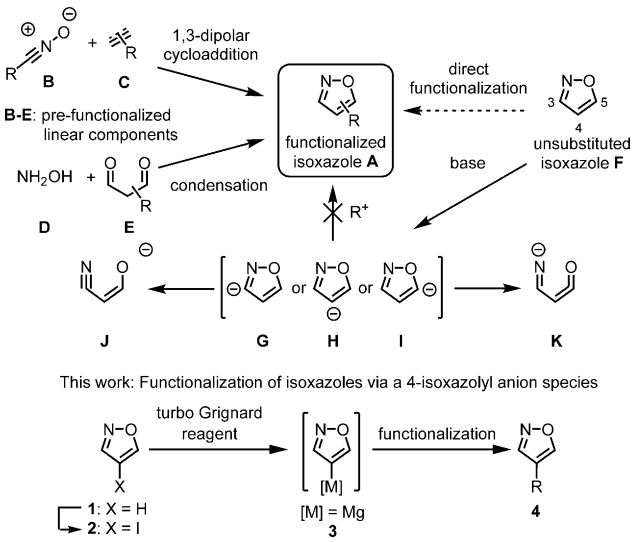
Abstract: *A direct functionalization of unsubstituted isoxazole (**1**) was achieved by generation of 4-isoxazolyl anion species (**3**). An efficient 4-iodination of isoxazole and halogen–metal exchange reaction using a turbo Grignard reagent (iPrMgCl·LiCl) were essential for the generation of **3**, which reacted with various electrophiles to give 4-functionalized isoxazoles in good to high yields. Isoxazolyl boronate, boronic acid, and stannane were also synthesized as useful building blocks from **1**. The current methods enabled us to synthesize multifunctionalized isoxazoles by introducing each substituent into the desired positions. Furthermore, total synthesis of triumferol, which was isolated from Triumfetta rhomboidea, was achieved from **1** in only three steps.*

Isoxazole is a five-membered heteroaromatic ring that was discovered by Claisen in 1888.[1] It is an important framework not only as a building block for natural product synthesis[2] but also as pharmaceuticals[3] and agrochemicals.[4] The fact that the isoxazole ring ranks 33rd among the 351 ring systems found in marketed drugs[5] has sparked a great deal of interest in the synthesis of functionalized isoxazoles. Various approaches have been reported for the synthesis of the functionalized isoxazoles **A**, including ring construction with the pre-functionalized linear components **B** with **C** and **D** with **E** by 1,3-dipolar cycloadditions and condensations, respectively (Scheme 1).[6] However, the direct functionalization of the unsubstituted isoxazole **F** has not been established because the isoxazolyl anions **G**–**I**, generated from **F** or its derivatives under basic conditions, readily afford the ring-opening products **J**[7] and **K**.[8] Nakanishi et al. reported that the attempt for preparation of **H** by metalation of 4-bromoisoxazole led to a complex mixture.[9] There is only one report of successful direct functionalization of the unsubstituted **F**. Boogaert and Nolan demonstrated a direct C–H carboxylation of **F** at the 5-position using an N-heterocyclic carbene gold complex without generating the labile isoxazolyl anion species.[10] Therefore, development of facile access to the substituted isoxazoles is required, particularly for isoxazole-based pharmaceuticals and agrochemicals. Although 3- and/or 5-substituted isoxazoles can be prepared by conventional ring construction approaches from



Scheme 1. Synthetic approaches for functionalized isoxazoles.

pre-functionalized linear components, the preparation of 4-substituted isoxazoles using these approaches is not a simple task, and the structural variation of the substituents is markedly dependent on the pre-functionalized linear components. Herein, we succeeded in the preparation of the 4-isoxazolyl anion species **3** from 4-iodoisoxazole (**2**; Scheme 1). The isoxazolyl anion species did not afford ring-opening products but enabled us to synthesize structurally diverse 4-substituted isoxazoles (**4**). Furthermore, we succeeded in the synthesis of multifunctionalized isoxazoles, step-by-step, by using the current 4-isoxazolyl anion method.

We first examined the generation of the desired 4-isoxazolyl anion by an iodine–metal exchange with **2**. However, the preparation of **2** was fraught with difficulty because the unsubstituted isoxazole **1** was not a good electron donor in the S_EAr reaction, because of the electronegativity of the oxygen atom. Indeed, the reported yield of the electrophilic aromatic iodination is only 11%.[11] Therefore, the electrophilic aromatic iodination of **1** at the 4-position was investigated, and the results are shown in Table 1. We first examined the iodination under the reported reaction conditions.[11] However, **2** was obtained in only 9% yield (entry 1). To enhance the electrophilicity of *N*-iodosuccinimide (NIS),[12] trifluoromethanesulfonic acid (TfOH) was used as the solvent (entry 2). The combination of NIS in TfOH afforded **2**, although the yield was not satisfactory. Similarly, a combination of 1,3-diiodo-5,5-dimethylhydantoin (DIH)[13] and *N*-iodosaccharin (NISac)[14] in either TfOH or TFA resulted in low yields (entries 3–6). Significant improvement was observed when the reaction was carried out under

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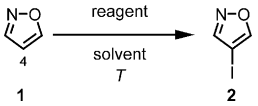
Table 1: Electrophilic aromatic iodination of unsubstituted isoxazole **1**.

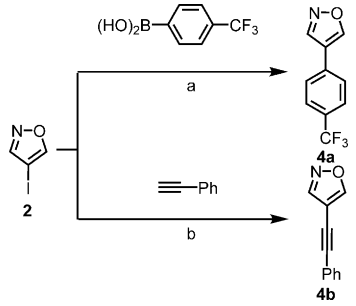


Entry	Reagent	Solvent	*T* [°C]	Yield [%][a]
1	NIS	TFA	50	9
2	NIS	TfOH	50	13
3	DIH	TfOH	50	2
4	DIH	TFA	50	29
5	NISac	TfOH	50	3
6	NISac	TFA	50	trace
7	NIS	TFA	120 (M.W.)	70
8	NIS	TFA	120 (M.W.)	69[b]

[a] Yield of isolated product. [b] The reaction was carried out at gram scale (ca. 2 g of product). M.W. = microwave, TFA = trifluoroacetic acid.

microwave irradiation conditions, and **2** was obtained in 70% yield (entry 7). To our delight, the yield of **2** was reproducible, even on a gram scale (entry 8). It should be noted that this is the first report of the electrophilic halogenation of **1** in such good yields.

With the establishment of a practical protocol for the synthesis of **2**, we next examined various chemical modifications of **2**, which should be valuable for functionalization at the 4-position using transition metal-catalyzed cross-coupling reactions. Therefore, we conducted typical palladium-catalyzed cross-coupling reactions, Suzuki–Miyaura coupling[15] and Sonogashira coupling,[16] with **2** (Scheme 2). As has been

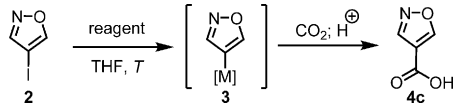


Scheme 2. Introduction of substituents at the 4-position of 4-iodoisoxazole (**2**) by palladium-catalyzed cross-coupling reactions. a) 5 mol% $[Pd_2(dba)_3]$,[17] 10 mol% $P(tBu)_3{\cdot}HBF_4$,[18] Na_2CO_3, THF/H_2O (1:1), RT, 1 h, 88%; b) 2 mol% $[PdCl_2(PPh_3)_2]$, 4 mol% CuI, 1.1 equiv NEt_3, THF, RT, 1 h, 64%. dba = dibenzylideneacetone, THF = tetrahydrofuran.

described before, 3,5-unsubstituted isoxazole is extremely labile under basic conditions. To suppress ring opening, Suzuki–Miyaura coupling was performed under two-phase conditions using Na_2CO_3 in THF and H_2O. As a result, the desired coupling product **4a** was obtained in a high yield (88%). Similarly, Sonogashira coupling using 1.1 equivalents of NEt_3 afforded the desired product **4b** in 64% yield.

We next examined the generation of the carbanion **3** from **2** and subsequent electrophilic trapping with CO_2 to obtain 4-isoxazolyl carboxylic acid (**4c**) for structurally diverse functionalization (Table 2). The iodine–metal exchange reaction

Table 2: Preparation of the 4-oxazolyl anion by halogen–metal exchange of **2**.



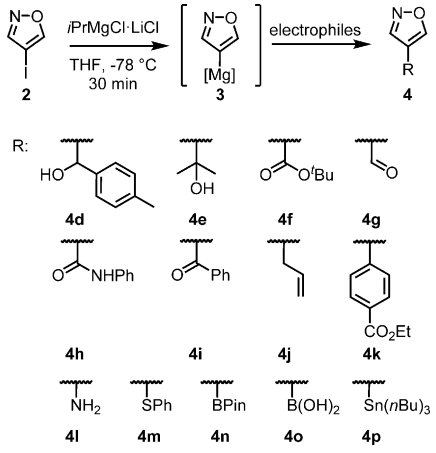
Entry	Reagent	Conc. of **2** [M]	*T* [°C]	Yield [%][a]
1	*n*BuLi	0.3	−78	–[b]
2	*i*PrMgCl·LiCl	1.0	−78	–[b]
3	*i*PrMgCl·LiCl	0.1	−78	quant.
4	*i*PrMgCl·LiCl	0.1	−20	quant.

[a] Yield of isolated product. [b] Complex mixture was obtained.

using *n*BuLi produced a complex mixture (entry 1). Then, turbo Grignard reagent (*i*PrMgCl·LiCl)[19] was used for the iodine–metal exchange reaction. The use of a 1.0 M solution of **2** again afforded a complex mixture (entry 2). However, surprisingly, the use of a lower concentration (0.1 M) of **2** and *i*PrMgCl·LiCl resulted in a dramatic improvement of the yield of **4c** (entry 3). The reaction was carried out as follows: to a stirred 0.1 M solution of **2** in THF, a 0.63 M solution of *i*PrMgCl·LiCl in THF (1.10 equiv) was added dropwise at −78 °C under an argon atmosphere. After being stirred at the same temperature for 30 minutes, the vessel was filled with CO_2 gas, which was collected in a balloon by sublimation of dry ice. After being stirred at room temperature for 15 minutes, a standard workup procedure afforded the desired product **4c** quantitatively. We speculated that heat generated when a higher concentration solution was used induced undesired reactions. However, even if the reaction was carried out at −20 °C, the desired product **4c** was obtained quantitatively (entry 4). Although the exact reason why the concentration of **2** was critical for this reaction is not clear, we suppose that the undesired ring opening of **2**, by the generated anion species **3**,[20] might be suppressed under the lower concentration conditions.

Additional functionalizations using **3** were investigated, as shown in Table 3. Various functional groups were introduced at the 4-position of isoxazole in good to excellent yields (52% to quant.). The nucleophilic addition reactions of **3** proceeded with various electrophiles, such as aldehyde (entry 1), ketone (entry 2), anhydride (entry 3), formamide (entry 4),[21] and isocyanate (entry 5) to give corresponding adducts **4d–h** in 55–88% yields. Acylation and allylation of **3** also proceeded in the presence of a catalytic amount of CuCN·2 LiCl (0.2 equiv) to give 4-benzoylisoxazole (**4i**; 52%) and 4-allylisoxazole (**4j**; 84%), respectively (entries 6 and 7). Not only the nucleophilic additions but also Negishi cross-coupling[22] with ethyl 4-iodobenzoate proceeded in the presence of $ZnCl_2$ (1.1 equiv) to afford ethyl 4-(4′-isoxazolyl) benzoate (**4k**) in 61% yield (entry 8). Furthermore, **3** underwent carbon–heteroatom bond formation reactions. 4-Aminoisoxazole (**4l**)[23] and 4-phenylthioisoxazole (**4m**) were obtained from propan-2-one *O*-tosyl oxime (64%)[24] and $PhSO_2SPh$ (82%), respectively (entries 9 and 10). The conversion of **3** into more stable organometallic species was also possible and the corresponding boronate ester **4n**,[25]

Table 3: Reaction of isoxazolyl anion with various electrophiles.

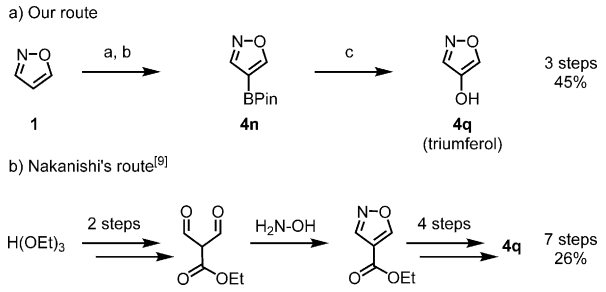


Entry	Electrophiles	Products	Yield [%][a]
1	*p*-tolualdehyde	**4d**	80
2	acetone	**4e**	55
3	Boc_2O	**4f**	88
4	DMF	**4g**	83
5	PhNCO	**4h**	64
6[b]	PhCOCl	**4i**	52
7[b]	allyl bromide	**4j**	84
8[c]	ethyl 4-iodobenzoate	**4k**	61
9[d]	propan-2-one *O*-tosyl oxime	**4l**	64
10	$PhSO_2SPh$	**4m**	82
11	BPin(O*i*Pr)	**4n**	90
12	$B(OMe)_3$	**4o**	quant.
13	$(nBu)_3SnCl$	**4p**	quant.

[a] Yield of isolated product. [b] CuCN·2 LiCl (0.2 equiv) was added. [c] $ZnCl_2$ (1.1 equiv) and 3 mol% [$Pd_2(dba)_3$], 6 mol% $PtBu_3{\cdot}HBF_4$ was added. [d] CuCN·2 LiCl (1.1 equiv) was added. Boc_2O = di-*tert*-butyldicarbonate, DMF = *N*,*N*-dimethylformamide, Pin = pinacolato.

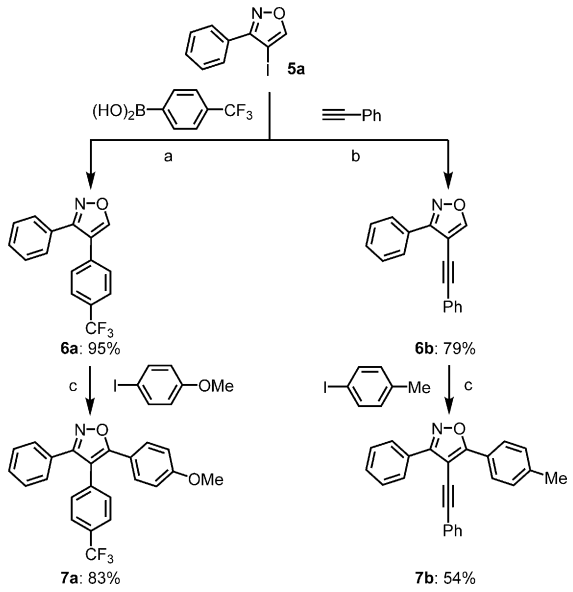
boronic acid **4o**, and tributylstananne **4p** were synthesized in excellent yields (90%-quant.; entries 11–13).

We attempted to synthesize 4-hydroxyisoxazole (**4q**; triumferol), which was isolated from *Triumfetta rhomboidea* in 1981 by Nakanishi and co-workers[9] and found to exert antigermination activity on lettuce seeds. Despite its simple structure, there is only one report of the synthesis of **4q** (Scheme 3b). The instability of 3,5-unsubstituted isoxazole under basic conditions makes the synthesis difficult to accomplish. We anticipated that a boryl group at the 4-position of **4n** could be converted into a hydroxy group under oxidative conditions.[26] As expected, treatment of **4n** with H_2O_2 and NaOH in THF/H_2O (10:1) afforded the desired **4q** in 71% yield. The undesired ring opening of the isoxazole ring was not observed under two-phase conditions. It should be noted that the synthesis of **4q** was accomplished with fewer steps and in a higher yield than that reported in the previous report (our route: 3 steps, 45% yield; Nakanishi's route: 7 steps, 26% yield).



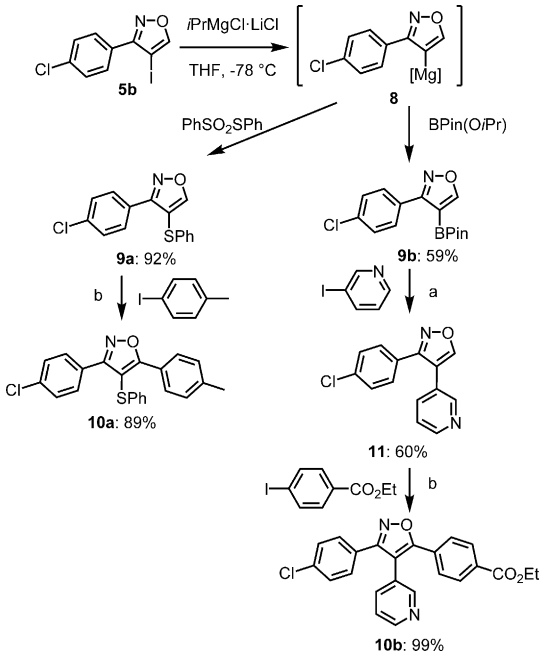
Scheme 3. Synthesis of 4-hydroxyisoxazole (**4q**) by our group (a), and by Nakanishi group (b). a) NIS, TFA, M.W. 120°C, 15 min. b) *i*PrMgCl·LiCl, THF, −78°C; BPin(O*i*Pr), 0°C, 4.5 h. c) H_2O_2, NaOH, THF/H_2O (10:1), RT, 30 min.

Because various functional groups were introduced into the 4-position of **1**, next we applied the current 4-isoxazolyl anion methods to the synthesis of multifunctionalized isoxazoles, where each substituent was introduced into the desired positions. Synthesis of the 3,4,5-trisubstituted isoxazoles **7a** and **7b** by sequential palladium-catalyzed cross-coupling reactions is shown in Scheme 4. 3-Phenylisoxazole, which was readily prepared from benzaldehyde, was converted into the iodide **5a** (for synthetic details see the Supporting Information), and then Suzuki–Miyaura coupling and Sonogashira coupling were performed with aryl boronic acid and phenylacetylene to afford **6a** (95%) and **6b** (79%), respectively. The C–H direct arylation at the 5-position of **6a** was carried out according to the literature procedure reported by Sasai et al.[27] and gave the triaryl-substituted isoxazole **7a** in 83% yield. The C–H direct arylation of **6b** also proceeded without affecting an alkynyl moiety in the molecule to afford trisubstituted isoxazole **7b** in 54% yield.



Scheme 4. Synthesis of 3,4,5-trisubstituted isoxazoles from 3-phenylisoxazole (**5a**) by sequential cross-coupling reactions. a) 3 mol% [$Pd_2(dba)_3$], 6 mol% $P(tBu)_3{\cdot}HBF_4$, Na_2CO_3, THF/H_2O (1:1), RT, 1.5 h; b) 2 mol% [$PdCl_2(PPh_3)_2$], 4 mol% CuI, 1.5 equiv NEt_3, THF, RT, 1 h; c) 15 mol% $Pd(OAc)_2$, 30 mol% dppBz, AgF, DMA, 100°C. dppBz = 1,2-bis(diphenylphosphino)benzene, DMA = *N*,*N*-dimethylacetamide.

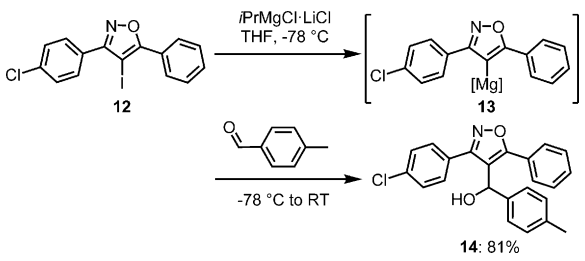
Next we investigated the generation of 3-substituted 4-isoxazolyl anion species **8** (Scheme 5). The 4-isoxazolyl anion



Scheme 5. Synthesis of trisubstituted isoxazoles **10** using isoxazolyl anion species **8**. a) 10 mol% $[Pd_2(dba)_3]$, 24 mol% $PCy_3{\cdot}HBF_4$, K_3PO_4, 1,4-dioxane/H_2O (2:1), 100°C, 18 h; b) 10 mol% $Pd(OAc)_2$, 20 mol% dppBz, AgF, DMA, 100°C, 20 h.

species **8**, selectively generated in the presence of a chlorophenyl group from **5b**, were trapped with $PhSO_2SPh$ and Bpin(O*i*Pr), and the corresponding thioether **9a** and boronate **9b** were obtained in 92 and 59% yields, respectively. The isoxazolyl boronate **9b** is a useful building block. Indeed, **9b** underwent Suzuki–Miyaura coupling reaction with 3-iodopyridine to afford the 3,4-diaryl-substituted isoxazole **11** in good yield (60%). Although both **9a** and **11** have the Lewis-basic functional groups such as thioether and pyridyl moieties, the C–H direct arylations proceeded smoothly to provide the trifunctionalized isoxazoles **10a** (89%) and **10b** (99%), respectively.

We also examined the nucleophilic addition of the sterically hindered 4-isoxazolyl anion species **13** to an aldehyde (Scheme 6). Although similar nucleophilic additions of isoxazolyl lithium containing phenyl groups, at the 3- and 5-positions, to benzaldehyde were reported by Orozco and coworkers, the yield of the desired adduct was only 15%, mainly because of the steric bulk of two aryl rings adjacent to the reaction site.[28] To our delight, **13**, prepared from the corresponding iodide **12**, reacted with *p*-tolualdehyde to give the desired adduct **14** in 81% yield.



Scheme 6. Generation of sterically hindered isoxazolyl anion species **13** and its addition reaction.

In summary, we designed a high-yielding and scalable synthesis of 4-iodoisoxazole and succeeded in the generation of its corresponding anion species by iodine–magnesium exchange reaction using a turbo Grignard reagent. The synthesis allowed us to introduce a wide variety of functional groups into the 4-position of the isoxazole ring in good to excellent yields. This protocol is the first practical and structurally diverse approach for functionalizing the unsubstituted isoxazole **1**. Furthermore, the current 4-isoxazolyl anion method enabled us to synthesize 3,4,5-trisubstituted isoxazoles by introducing each substituent into the desired positions in a step-by-step manner. It is not an easy task to synthesize multifunctionalized isoxazoles because of the difficulty in introducing substituents at the 4-position of isoxazoles by other conventional methods. In addition, a short-step synthesis of 4-hydroxyisoxazole (triumferol) was achieved in a high yield. As the current approach provides various isoxazolyl metal species, such as magnesium, boron, and stannane, we can envision a wide variety of transformations using these isoxazolyl metal species in organic synthesis. Further functionalization using these isoxazolyl metal species is ongoing in our laboratory.

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