JOC*Note*

Magnesiation of Pyridine *N*-Oxides via Iodine or Bromine−Magnesium Exchange: A Useful Tool for Functionalizing Pyridine *N*-Oxides

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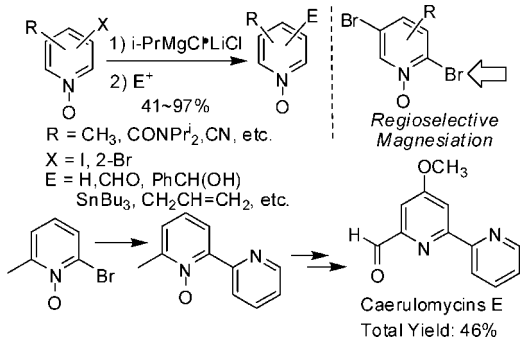

Iodo- or 2-bromopyridine *N*-oxides were readily magnesiated with *i*-PrMgCl·LiCl via the iodine or bromine−magnesium exchange. The bromine adjacent to pyridine *N*-oxide (at the 2- or 6-position) can be regioselectively magnesiated in the presence of other position substituted halogens. This method was tested in various substituted pyridine *N*-oxide systems, and has been successfully applied to the total synthesis of caerulomycins E and A.

Pyridine *N*-oxide[1] has received wide attention as a synthetic intermediate, oxidant,[2] catalyst, and ligand.[3] In addition, some of the related compounds are also of important biological or pharmaceutical activities.[4] Pyridine *N*-oxides have been utilized as an important tool to functionalize the pyridine ring including nitration, halogenation, and cyanation.[1] For example, considerable efforts have been reported recently in the conversion of the *N*-oxides into (a) 2-aminopyridine with Ts_2O-^{t}BuNH$_2$ followed by in situ deprotection with TFA,[5] (b) 2-aminopyridine amides with imidoyl chlorides,[6] (c) tetrazolopyridines with sulfonyl or phosphoryl azides[7] and imidazolopyridines with sulfuryl diimidazole,[8] (d) 2-alkyl, alkynyl, and arylpyridines with Grignard reagents,[9] and (e) 3-(2-hydroxyaryl)pyridines with arynes.[10] It is noteworthy that pyridine *N*-oxides also served as an ideal choice to direct C−H functionalization of the pyridine ring.[11] Currently the pyridine *N*-oxides preparation is mainly focused on the oxidation of corresponding pyridine analogues. To this end, an alternative approach was described herein to prepare the pyridine *N*-oxide derivatives via direct functionalization without deoxygenation.

Metalation of substituted pyridines has been well investigated;[12] however, only limited examples were reported regarding the metalation of pyridine *N*-oxides, through either lithium or zinc reagents.[13,14] One of the challenges in lithiation with use of *n*-BuLi, LDA, or LTMP is unwanted deprotonation of the side chain if it is present at the pyridine *N*-oxide 2- or

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(5) Yin, J.; Xiang, B.; Huffman, M. A.; Raab, C. E.; Davies, I. W. *J. Org. Chem.* **2007**, *72*, 4554.

(6) (a) Manley, P. J.; Bilodeau, M. T. *Org. Lett.* **2002**, *4*, 3127. For a similar conversion of quinoline *N*-oxides, see: (b) Couturier, M.; Caron, L.; Tumidajski, S.; Jones, K.; White, T. D. *Org. Lett.* **2006**, *8*, 1929.

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(8) Keith, J. M. *J. Org. Chem.* **2008**, *73*, 327.

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(10) Raminelli, C.; Liu, Z.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 4689.

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(12) For reviews, see: (a) Chinchilla, R.; Nájera, C.; Yus, M. *ARKIVOC* **2007**, *12*, 152. (b) Mulvey, R.; Mongin, F.; Uchiyama, M.; Kondo, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 3802. (c) Schlosser, M.; Mongin, F. *Chem. Soc. Rev.* **2007**, *36*, 1161. (d) Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4059. For a recent report, see: (e) Seggio, A.; Chevallier, F.; Vaultier, M.; Mongin, F. *J. Org. Chem.* **2007**, *72*, 6602.

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(14) Hlavinka, M. L.; Hagadorn, J. R. *Organometallics* **2007**, *26*, 4105.

10.1021/jo802172f CCC: $40.75
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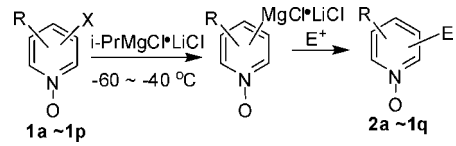
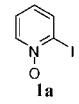
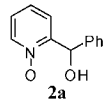
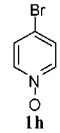
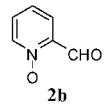
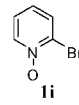
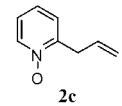
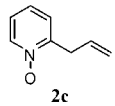
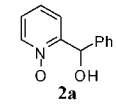
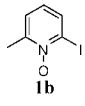
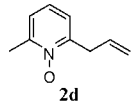
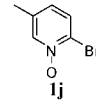
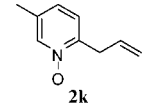
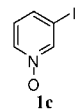
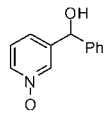
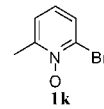
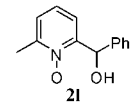
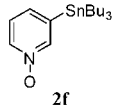
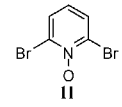
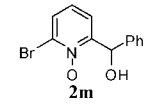
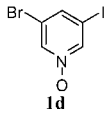
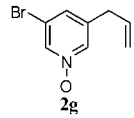
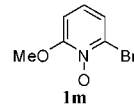
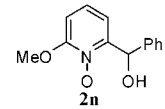
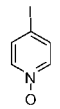
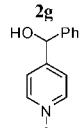
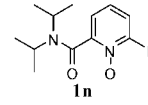
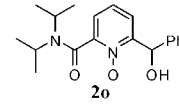
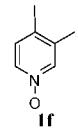
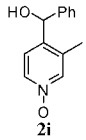
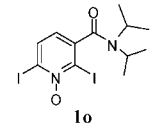
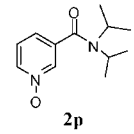
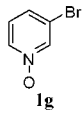
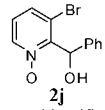
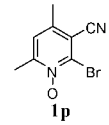
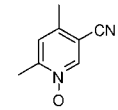
TABLE 1. Magnesiation of Iodo- or 2-Bromopyridine *N*-Oxide Derivatives[a]



Entry	Oxide	Eletrophile	Product	Yield(%)[b]	Entry	Oxide	Eletrophile	Product	Yiled(%)[b]
1	 **1a**	PhCHO	 **2a**	90	11	 **1h**	PhCHO	unidentified complex mixture	--
2	**1a**	$HCONMe_2$	 **2b**	76	12	 **1i**	Allyl bromide	 **2c**	66[c]
3	**1a**	Allyl bromide	 **2c**	85[c]	13	**1i**	PhCHO	 **2a**	41
4	 **1b**	Allyl bromide	 **2d**	96[c]	14	 **1j**	Allyl bromide	 **2k**	63[c]
5	 **1c**	PhCHO	 **2e**	60	15	 **1k**	PhCHO	 **2l**	75
6	**1c**	Bu_3SnCl	 **2f**	62	16	 **1l**	PhCHO	 **2m**	87
7	 **1d**	Allyl bromide	 **2g**	67[c]	17	 **1m**	PhCHO	 **2n**	67
8	 **1e**	PhCHO	 **2h**	75	18	 **1n**	PhCHO	 **2o**	89[e]
9	 **1f**	PhCHO	 **2i**	72	19	 **1o**	H_2O	 **2p**	91[f]
10	 **1g**	PhCHO	 **2j** + unidentified complex mixture	28[d]	20	 **1p**	H_2O	 **2q**	97[e]

[a] The reactions were carried out at −40 °C for entries 1−17 and −60 °C for entries 18−20. [b] Isolated yield. [c] The Grignard reagent was transmetalated with CuI·2LiCl before reacting with allyl bromide. [d] Isolated yield of **2j**. [e] The oxides were hardly dissoluble in THF and CH_2Cl_2 was used as a cosolvent. [f] 2.1 equiv of *i*-PrMgCl·LiCl was used during the exchange reaction.

6-position.[14,15] To this regard, Grignard reagent was employed here as an alternative metalation agent helping to improve chemoselectivity and eliminate the aforementioned side products. Magnesiation of pyridine *N*-oxides was carried out through either iodine or bromine−magnesium exchange in the Knochel's manner.[16]

2-Iodopyridine *N*-oxide (**1a**) and PhCHO were chosen as the substrates, and an array of Grignard reagents were tested, including *i*-PrMgBr, *i*-PrMgCl, and *i*-PrMgCl·LiCl. Initial

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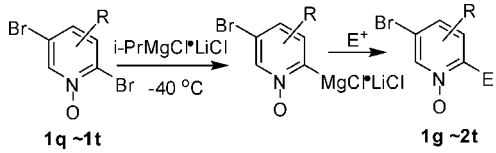
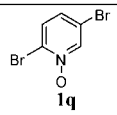
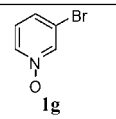
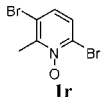
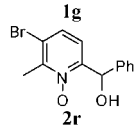
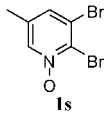
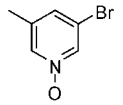
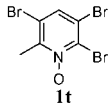
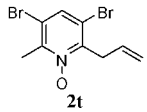
TABLE 2. Regioselective Magnesiation of Di- or Tribromopyridine *N*-Oxides[a]

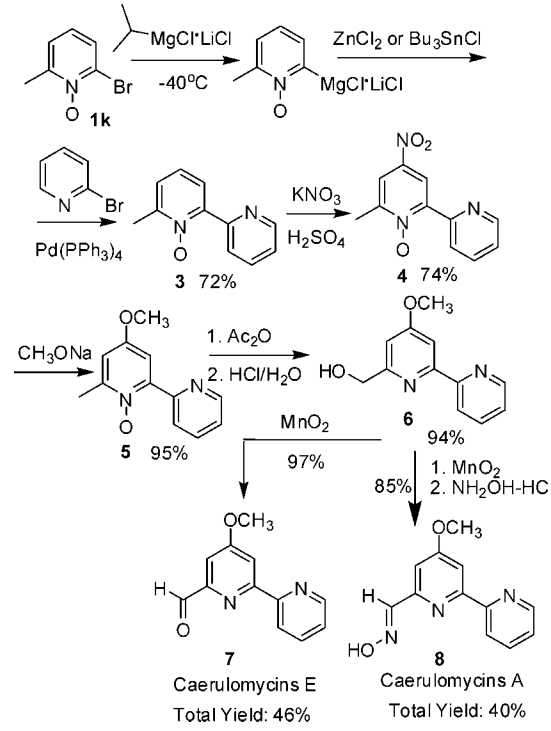


Entry	Oxide	Electrophile	Product	Yield[b] (%)
1	 1q	H_2O	 1g	49[c]
2	 1r	PhCHO	 2r	89
3	 1s	H_2O	 2s	96
4	 1t	Allyl bromide	 2t	94[d]

[a] The reactions were carried out at −40 °C. [b] Isolated yield. [c] No 2-bromopyridine *N*-oxide was observed in our hands. [d] The Grignard reagent was transmetalated with CuI·2LiCl before reacting with allyl bromide.

results showed that reaction proceeded rapidly and exclusively with *i*-PrMgCl·LiCl (within 1−2 h). The optimal magnesiation temperature was found to be between −40 and −60 °C, while a higher temperature led to reaction of the Grignard reagent with the oxide.[9] Next a series of iodo- or bromopyridine *N*-oxides were examined by using *i*-PrMgCl·LiCl at −40 °C and the results are summarized in Table 1. In general, 2(or 6)-, 3- (or 5-), and 4-iodopyridine *N*-oxide derivatives can be efficiently magnesiated (Table 1, entries 1−9). However, corresponding metalation of 3(or 5)-, 4-bromopyridine *N*-oxides with bromine−magnesium failed to give the desired products (Table 1, entries 10 and 11). Instead, two side reactions were observed: (a) the reaction of *i*-PrMgCl·LiCl with the oxides leading to a dienal oxime as reported[9] and (b) the deprotonation of 2(or 6-)-hydrogen (e.g., **2j**). As expected, 2(or 6)-bomopyridine *N*-oxide derivatives were successfully magnesiated through a bromine−magnesium exchange (Table 1 entries 12−17). Slightly better yields were obtained with 6-substituted-2-bomopyridine *N*-oxides (Table 1 entries 15−17). Under this magnesiation condition, good yields were also obtained for the pyridine *N*-oxide system tethered with electrophilic functional

SCHEME 1. Total Synthesis of Caerulomycins E and A



groups, such as amide or cyano (Table 1, entries 18−20). Unlike the lithiation conditions,[14] no deprotonation of a 2(or 6)-methyl group was observed (Table 1, entries 2, 15, and 20). Using this convenient and mild metalation condition, various CH═O, C═C containing pyridine *N*-oxides were prepared (Table 1, entries 2−4, 7 and 12), which otherwise are not readily available via traditional oxidation conditions.

Regioselective metalation of 2,5-dibromopyridine via metal−bromine exchange has been studied extensively.[17] Magnesiation was reported to occur selectively at the C(5) position, using bromine−magnesium based reactions.[17g−k] Selective metalation could be achieved at the 2-position via lithiation under harsh conditions,[17c−e] or iodine−magnesium exchange with the corresponding 5-bromo-2-iodopyridine.[17j] In light of the promising results obtained in Table 1, we were prompted to explore the selective magnesiation at the 2(or 6)-position of pyridine *N*-oxides based on the strong inductive effect from *N*-oxide. Substituted di- or tribromopyridine *N*-oxides were chosen as the substrates and the results were outlined in Table 2. Our study clearly indicated that the di- or tribromopyridine *N*-oxides can be selectively magnesiated at the 2 (or 6)-position under mild conditions. This has provided an alternative route to selectively magnesiate the 2(or 6)-position of pyridine system.

Utilizing the aforementioned magnesiation condition to functionalize the pyridine 2-position, we have successfully completed the total synthesis of two naturally occurring 2,2′-bipyridyl compounds, caerulomycins E and A (Scheme 1).[18] Compound 2-bromo-6-methylpyridine *N*-oxide (**1k**) was first magnesiated and transmetalated with $ZnCl_2$ or Bu_3SnCl. It was then coupled with 2-bromopyridine in situ under Pd-mediated Negishi or Stille conditions to yield key 2,2′-bipyridyl intermediate **3** in 72% yield. It is noteworthy that this synthetic approach also provides a general method to prepare mono *N*-oxide of unsymmetrical 2,2′-bipyridyl compounds.

Nitration of 6-methyl-2,2-bipyridine *N*-oxide (**3**) gave **4** followed by nucleophilic substitution of sodium methoxide to

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yield 4-methoxy-2,2-bipyridine *N*-oxide (**5**). Treatment of **5** with Ac_2O, followed by hydrolysis led to (4-methoxy-2,2′-bipyridin-6-yl)methanol (**6**). With the further modification of **6**, Caerulomycins E and A were synthesized with an overall yield of 46% and 40%, respectively. This represented a significant improvement compared with those reported previously (caerulomycins E: Quéguiner's six-step synthesis from 2,2′-bipyridine, an overall yield of 26%;[18a] caerulomycins A: Quéguiner's synthesis from 2,2′-bipyridine, 20% yield;[18a] Divekar's two-step synthesis from 4-methoxy-2,2′-bipyridine *N*-oxide, 8% yield;[18d] De Souza's four-step synthesis, 5% yield[18c]). In addition, the reagents used in our synthesis are readily available and corresponding procedures are very straightforward.

In conclusion, for the first time magnesiation of pyridine *N*-oxides via an iodine or bromine−magnesium exchange was achieved. This metalation provides a very useful tool to functionalize the pyridine *N*-oxides without deoxygenation. This methodology has enabled us to achieve (1) convenient preparations of a series of the *N*-oxides that are not readily obtained, (2) regioselective magnesiation of di- or tribromopyridine *N*-oxides at the 2(or 6)-position in the presence of 3(or 5)-bromine(s), and (3) efficient synthesis of a mono pyridine *N*-oxide of an unsymmetrical 2,2′-bipyridyl compound, leading to a facile total synthesis of Caerulomycins E and A. Furthermore, this magnesiation also extends the scope of Knochel's Grignard reagent preparation.

Experimental Section

General Procedure for Magnesiation of Iodo- or Bromopyridine Pyridine *N*-Oxides and Reaction with Electrophile. Under argon, a four-necked flask equipped with a magnetic stirrer was charged with pyridine *N*-oxide (6 mmol) in 40 mL of THF. The mixture was cooled to −60 to −40 °C, and *i*-PrMgCl·LiCl (prepared and titrated according to the reported procedure,[19] 6.3 mmol) was added slowly with a syringe while the reaction temperature was kept under −40 °C. The mixture was stirred at −60 to −40 °C until starting material was consumed (monitored by TLC). In the case of transmetalation (Table 1, entries 3, 4, 7, 12, 14, and Table 2, entry 4), a solution of CuI·2LiCl in THF (6.3 mmol) was added with a syringe and the resulting mixture was stirred at −60 to −40 °C for 20 min. The electrophile reagent (7 mmol) was then added and it was stirred under the same temperature until starting material was fully consumed (monitored by TLC). The reaction was quenched with 10% aqueous NH_4Cl solution and taken up with CH_2Cl_2. The organic layer was collected and concentrated. The resulting crude material was purified by flash chromatography to give the desired products. Note: When H_2O was used as an electrophile, the reaction was quenched directly.

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Supporting Information Available: Typical experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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