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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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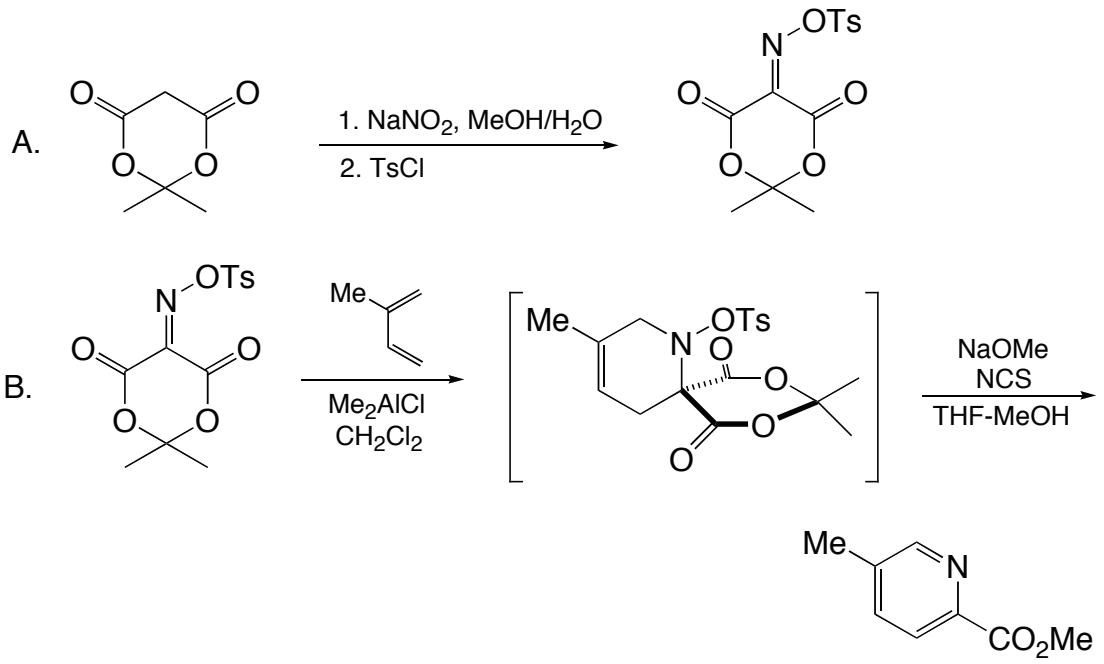
PREPARATION OF SUBSTITUTED PYRIDINES VIA REGIOCONTROLLED [4 + 2] CYCLOADDITIONS OF OXIMINOSULFONATES: METHYL 5-METHYLPYRIDINE-2-CARBOXYLATE

[(2-Pyridinecarboxylic acid, 5-methyl-, methyl ester)]



Submitted by Rick L. Danheiser, Adam R. Renslo, David T. Amos, and Graham T. Wright.[1]
Checked by Helga Krause and Alois Fürstner.

1. Procedure

A. 5-(Tosyloxyimino)-2,2-dimethyl-1,3-dioxane-4,6-dione. A 100-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, magnetic stirring bar, rubber septum, and solid addition funnel fitted with a rubber septum (Note 1) is charged with 4.00 g (27.8 mmol) of Meldrum's acid (Note 2) and 23 mL of methanol (Note 3). To this suspension is added in one portion a solution of 1.91 g (27.8 mmol) of sodium nitrite (Note 4) in 15 mL of water. The reaction mixture is stirred for 2 h at room temperature to give a deep red solution which is then treated with 4 mL of pH 7 phosphate buffer (Note 5) in one portion and then cooled to 0 °C. *p*-

Toluenesulfonyl chloride (4.81 g, 25.2 mmol) (Note 6) is added over 3 min via the solid addition funnel and the cooling bath is removed. The resulting peach-colored mixture is vigorously stirred for 30 min, then the solids are collected by filtration on a Büchner funnel with the aid of 40 mL of cold methanol. The resulting solids are dried at 0.2 mm in a desiccator over phosphorus pentoxide (P_2O_5) for 4 h to provide 4.85 g (56-59% based on TsCl) of the oximinosulfonate as a white solid, mp 155-156 °C (Note 7).

B. Methyl-5-methylpyridine-2-carboxylate. A 250-mL, three-necked, round-bottomed flask, equipped with an argon inlet adapter, magnetic stirring bar, rubber septum, and pressure-equalizing addition funnel fitted with a rubber septum (Note 8), is charged with a solution of 4.50 g (13.7 mmol) of oximinosulfonate in 100 mL of dichloromethane (Note 9) and 4.10 mL (2.81 g, 41.1 mmol) of isoprene (Note 10). The solution is cooled at −78 °C while 27.5 mL (27.5 mmol) of a 1.0M solution of dimethylaluminum chloride (Me_2AlCl) in hexane (Note 11) is added dropwise via the addition funnel over 9 min. The resulting orange solution is stirred for 3 h at −78 °C to give a yellow solution which is then quenched by the addition of 60 mL of saturated sodium potassium tartrate solution in one portion. The resulting mixture is allowed to warm to 0 °C over 30 min, then is transferred to a 500-mL separatory funnel. Dichloromethane (80 mL) and 150 mL of water are added, and the aqueous phase is separated and extracted with three 80-mL portions of dichloromethane. The combined organic phases are washed with 80 mL of saturated sodium chloride solution, dried over magnesium sulfate ($MgSO_4$), filtered, and concentrated at reduced pressure on a rotary evaporator to provide 5.48-5.54 g of cycloadduct as an orange foam which is used in the next step without further purification (Notes 12, 13).

A 250-mL, round-bottomed flask equipped with an argon inlet adapter and magnetic stirring bar (Note 8) is charged with a solution of the crude cycloadduct prepared above in 80 mL of tetrahydrofuran (Note 14) and 80 mL of methanol (Note 3). The solution is cooled at 0 °C while 26.3 mL (41.1 mmol) of a 1.56M solution of sodium methoxide (NaOMe) in methanol (Note 15) is added via syringe over 4 min followed by the addition of 1.83 g (13.7 mmol) of *N*-chlorosuccinimide (Note 16) in one portion. The cooling bath is removed, and the resulting yellow solution is stirred in the dark for 16 h (Note 17). The reaction mixture is concentrated to a volume of ca. 20 mL by rotary evaporation, then diluted with 150 mL of ethyl acetate

and 150 mL of pH 7 phosphate buffer (Note 5). The aqueous phase is separated and extracted with three 100-mL portions of ethyl acetate, and the combined organic phases are extracted with three 100-mL portions of 1.0N HCl. The combined aqueous extracts are neutralized by the slow addition of solid sodium bicarbonate (Note 18), then extracted with three 100-mL portions of ethyl acetate. The combined organic phases are washed with 100 mL of saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated at reduced pressure on a rotary evaporator to afford 1.61-1.76 g (78-85%) of methyl 5-methylpyridine-2-carboxylate as a yellow solid, mp 47-49 °C (Notes 19-22).

2. Notes

1. The apparatus is purged with argon and maintained under an atmosphere of argon during the course of the reaction.

2. 2,2-Dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) was purchased from Aldrich Chemical Co., Inc. and recrystallized before use according to the following procedure. Meldrum's acid (10 g) was dissolved in a minimum amount of warm (40-45 °C) acetone (ca. 20 mL). Room temperature water (15 mL) was then added in one portion, resulting in the immediate precipitation of white needles which were collected by filtration on a Büchner funnel and dried (ca. 0.05 mm) in a desiccator over P_2O_5 overnight.

3. Anhydrous grade methanol was purchased from Mallinkrodt, Inc. and used as received.

4. Sodium nitrite was purchased from Mallinkrodt, Inc. and used as received.

5. Phosphate buffer (pH 7.00) was purchased from VWR Scientific Products, Inc; the checkers used phosphate buffer purchased from Riedel-de Haen.

6. *p*-Toluenesulfonyl chloride (TsCl) was purchased from Fluka Corporation and recrystallized before use according to the following procedure. TsCl (30 g) was dissolved in a minimum amount (ca. 50 mL) of warm (55-60 °C) chloroform to give a yellow solution. To this solution was added 70 ml of warm petroleum ether and 3 g of activated charcoal. After stirring for 10 min, the mixture was filtered and concentrated to half volume.

Crystals of TsCl precipitated and after 30 min were collected by filtration on a Büchner funnel. Drying at 0.05 mm for 1 h afforded 22 g of TsCl as white crystals, mp 67-68 °C.

7. The oximinosulfonate has the following spectroscopic properties: IR ($CHCl_3$) cm^{-1}: 3020, 1790, 1765, 1596, 1400, 1290; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.78 (s, 6 H), 2.46 (s, 3 H), 7.40 (d, 2 H, J = 8.4), 7.93 (d, 2 H, J = 8.4); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.8, 28.1, 106.8, 129.5, 130.1, 130.2, 138.8, 147.1, 149.6, 154.7. Anal. Calcd for $C_{13}H_{13}NO_7S$: C, 47.70; H, 4.00; N, 4.28; Found: C, 47.76; H, 4.02; N, 4.22.

8. The apparatus is flame-dried under reduced pressure and then maintained under an atmosphere of argon during the course of the reaction.

9. Dichloromethane was purchased from J.T. Baker, Inc. and purified by pressure filtration through activated alumina.

10. Isoprene was purchased from Aldrich Chemical Co., Inc. and distilled under argon at atmospheric pressure immediately before use.

11. Dimethylaluminum chloride in hexanes (1.0M) was purchased from Aldrich Chemical Company, Inc.

12. A pure sample of the intermediate cycloadduct can be obtained by column chromatography on silica gel (elution with 1% methanol/dichloromethane). The cycloadduct exhibits the following spectroscopic properties: IR ($CHCl_3$) cm^{-1}: 3020, 1780, 1750, 1385, 1300; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.67 (s, 3 H), 1.69 (s, 3 H), 1.88 (s, 3 H), 2.48 (s, 3 H), 2.71 (br dd, 2 H, J = 1.2, 3.3), 3.93 (s, 2 H), 5.33 (br., 1H), 7.36 (d, 2H, J = 7.9), 7.81 (d, 2 H, J = 8.4); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.3, 21.7, 28.5, 29.3, 32.8, 57.4, 66.3, 106.2, 113.9, 129.2, 129.55, 129.62, 131.2, 145.9, 164.0.

13. *CAUTION:* The checkers experienced a rather vigorous decomposition of this product upon evaporating the solvent in the rotary evaporator and drying of the crude material at 39 °C (bath temperature) and 15 mm. No hazards, however, were encountered when this operation was carried out at ambient temperature (22 °C) at 38 mm. The resulting crude material was directly used in the next step.

14. Tetrahydrofuran was purchased from J.T. Baker, Inc. and purified by pressure filtration through activated alumina.

15. A 1.56M solution of sodium methoxide was prepared by careful addition of 2.69 g of sodium metal (cut into ca. 15 pieces) to 75 mL of methanol at 0 °C under an atmosphere of argon.

16. *N*-Chlorosuccinimide (NCS) was purchased from Aldrich Chemical Company, Inc. and recrystallized before use according to the following procedure. NCS (25 g) was dissolved in 125 mL of glacial acetic acid at 60-65 °C in a 250-mL, Erlenmeyer flask and the resulting solution was allowed to cool to room temperature. The Erlenmeyer flask was then placed in an ice-water bath (15-20 °C), and white flakes of NCS immediately precipitated and were collected by filtration on a Buchner funnel (washing with 20-mL of glacial acetic acid and then with two 20-mL portions of hexanes) and then dried at 0.5 mm for 6 h and stored in the dark until use.

17. For this purpose, the flask was wrapped in aluminum foil.

18. Sodium bicarbonate was added until gas evolution was no longer observed.

19. The purity of this material was confirmed by spectroscopic and elemental analysis: IR (KBr) cm^{-1}: 3091, 3048, 3004, 2956, 1730, 1591, 1448, 1320, 1251, 1126, 1032, 781, 704; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.43 (s, 3 H), 4.00 (s, 3H), 7.64 (dd, 1 H, J = 7.8, 2.0), 8.05 (d, 1 H, J = 8.3), 8.57 (d, 1 H, J = 2.0); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.5, 52.6, 124.6, 137.1, 137.3, 145.2, 150.2, 165.6. Anal. Calcd for $C_8H_9NO_2$: C, 63.56; H, 6.00; N, 9.27; Found: C, 63.21; H, 6.02; N, 9.43; TLC: R_f = 0.11 (elution with 25% ethyl acetate-hexanes; phosphomolybdic acid in ethanol stain).

20. If desired, further purification can be effected by chromatography (Note 21) or, alternatively, by recrystallization according to the following procedure: the crude product is dissolved in 20 mL of warm (50 °C) hexanes and the solution is decanted from an insoluble orange solid and transferred to a 50-mL, round-bottomed flask. Concentration provides 1.34 g (65%) of methyl 5-methylpyridine-2-carboxylate as a colorless solid, mp 53-54 °C.

21. Purification by column chromatography was carried out according to the following procedure: silica gel (10 g) is added to the dried solution of crude product obtained from the work up, and the solution is concentrated by rotary evaporation to afford a free-flowing powder which is placed at the top of a column (4.5 cm diameter) of 40 g of silica gel (230-400 mesh) and eluted with 25% ethyl acetate/hexane (containing 1%

triethylamine) to afford 1.47 g (71%) of methyl 5-methylpyridine-2-carboxylate as a pale yellow solid, mp 54-55 °C.

22. The checkers obtained the crude material as a yellow-brown syrup (1.86 g, 89%). Column chromatography as described in (Note 21) afforded 1.29 g (63%) of the title compound as a pale yellow solid, mp 52-53 °C.

Waste Disposal Information

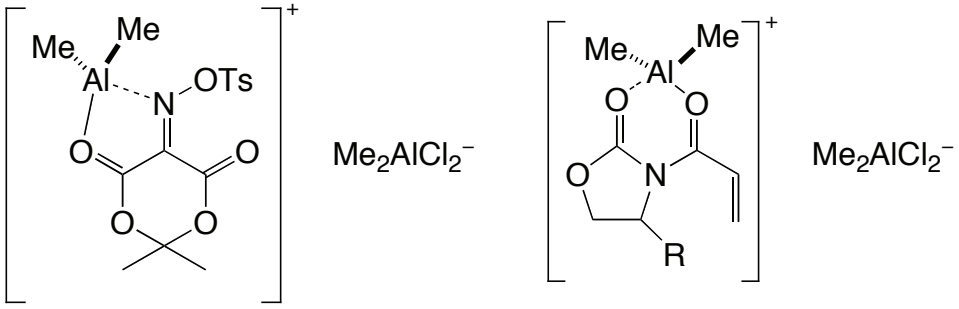
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The structures of a number of natural products incorporate the pyridine ring as do important commercial compounds including herbicides, insecticides, fungicides, and a variety of medicinal agents. Among the numerous strategies that have been developed for pyridine synthesis,[2] methods based on the Diels-Alder reaction are particularly attractive due to their intrinsic convergent character and regiochemical features. Although a variety of azadienophiles[3] have been used for the synthesis of tetrahydropyridines, few examples of their application in the synthesis of pyridines have previously been reported. The current procedure illustrates a versatile method for the synthesis of substituted pyridines via [4+2] cycloaddition of an oximinosulfonate derived from Meldrum's acid with conjugated dienes. Diels-Alder reactions of this new azadienophile are subject to Lewis acid promotion, permitting highly regioselective cycloadditions with a wide range of diene substrates under relatively mild reaction conditions.

As described here, we have developed a simple procedure that delivers multigram quantities of the key oximinosulfonate in good yield and excellent purity in one operation without the need for additional purification.[4] The oximinosulfonate is an easily handled solid that can be transferred in air and is stable for months when stored under argon in a refrigerator. Reaction of the oximinosulfonate with a conjugated diene and 2

equiv of Me_2AlCl leads to an efficient Diels-Alder reaction, providing cycloadducts which can then be transformed to substituted pyridines in a single synthetic operation. Significantly, the regiochemical course of the cycloaddition is opposite to that observed with conventional imino dienophiles, thus producing heterocycles with substitution patterns that cannot be accessed using prior imino-dienophile Diels-Alder methodology. A series of experiments in which the Me_2AlCl stoichiometry was varied from 0.1-2.5 equivalents established the requirement that a full 2.0 equiv of the Lewis acid be employed. As shown below, it is likely that the second equiv of Me_2AlCl serves to promote the ionization of chloride from an initial 1:1 Lewis acid complex and thereby generate the more reactive ionic 2:1 complex.[5,6]

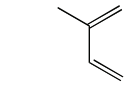
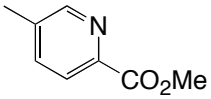
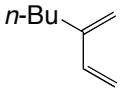
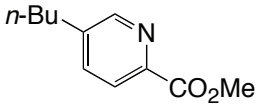
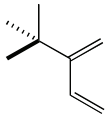
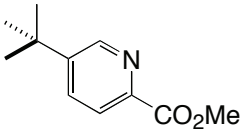
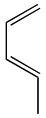
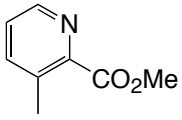
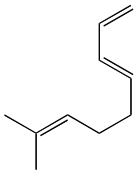
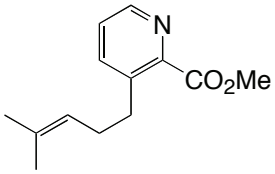
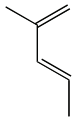
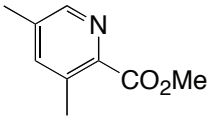
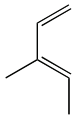
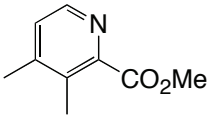
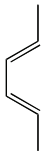
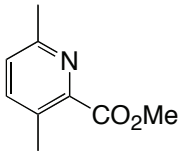
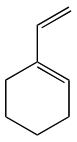
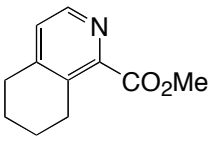
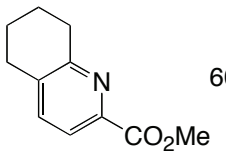


The cycloadducts obtained in the oximinosulfonate Diels-Alder reaction are best converted directly to pyridines without purification. Exposure of the spiro-fused cycloadducts to a combination of NCS and sodium methoxide brings about cleavage of the dioxanedione ring with concomitant elimination of acetone and carbon dioxide. Elimination of tosylate from the resulting ester enolate then generates a dihydropyridine, and subsequent chlorination by NCS and elimination of HCl finally provides the desired aromatic pyridine product.

The Lewis acid-promoted reaction of our oximinosulfonate with dienes and the conversion of the resulting cycloadducts to pyridines comprises a new annulation method for the synthesis of substituted pyridines from conjugated dienes. As illustrated in the Table, very good overall yields are obtained in reactions of 2-substituted dienes, providing 5-substituted pyridine-2-carboxylates. Reactions with 1-substituted dienes yield 3-substituted pyridines, and disubstituted dienes react smoothly to afford

trisubstituted pyridines in good yield. Polycyclic systems are obtained when dienes such as 1-vinyl-1-cyclohexene are employed in the annulation.

TABLE
[4+2] Pyridine Annulations[a]

diene[b]	pyridine	% yield[c]
		78-85
		72
		73
		56-57
		60
		70
		40
		40[d]
	  83 : 17	60

[a]Conditions: (a) oximinosulfonate, 2.0 equiv Me_2AlCl, CH_2Cl_2, −78 °C, 2-4 h; (b) 3.0 equiv MeONa, 1.0 equiv NCS, MeOH-THF (1:1), rt, 14-16 h. [b]1.5-3.0 equiv of diene was employed. [c]Isolated over all yield for two steps. [d]5.0 equiv of NaOMe and 4.0 equiv of NCS were used.

1. Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139. We thank the National Institutes of Health (GM 28273) for generous financial support. D.T.A. was supported in part by NIH training grant CA 09112.

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Methyl 5-methylpyridine-2-carboxylate: 2-Pyridinecarboxylic acid, 5-methyl-, methyl ester (9); (260998-85-4)

5-(Tosyloxyimino)-2,2-dimethyl-1,3-dioxane-4,6-dione: 1,3-Dioxane-4,5,6-trione, 2,2-dimethyl-, 5-*O*-[(4-methylphenyl)sulfonyl]oxime (9); (215436-24-1)

Meldrum's acid: 1,3-Dioxane-4,6-dione, 2,2-dimethyl- (9); (2033-24-1)

Sodium nitrite: Nitrous acid, sodium salt (8, 9); (7632-00-0)

p-Toluenesulfonyl chloride: Benzenesulfonyl chloride, 4-methyl- (9); (98-59-9)

Isoprene: 1,3-Butadiene, 2-methyl- (9); (78-79-5)

Dimethylaluminum chloride: Aluminum, chlorodimethyl- (8, 9); (1184-58-3)

N-Chlorosuccinimide: 2,5-Pyrrolidinedione, 1-chloro- (9); (128-09-6)