1:2:1 which remained unaltered by long periods of heating. This observation refers to an equilibrium reaction involving the pyridylthio radical, i.e., cleavage of the carbon–sulfur bond of 1, which also applies to the reaction of 1 with 2 at the same reaction temperature. However, no disproportionation reaction occurred between diphenyl sulfide (14) and substituted diphenyl sulfide, which indicates that no carbon–sulfur bond of 14 or substituted diphenyl sulfide cleaves upon heating. This observation is responsible for the fact that 2 did not react with substituted diphenyl sulfide. It may be concluded that the sulfide becomes feasible to react with 2, only when carbon–sulfur bond of the sulfide cleave upon heating. That is to say, favorable release of the pyridylthio group from the pyridine ring may enable the positional selectivity of the ipso substitution in 1. If the reactivity of 1 with 2 is attributed to polar effects of substrate, 9 must also undergo the similar reaction as 1 even slightly because the polar effect of nitrophenyl group does not differ too greatly from pyridyl group. Thus, it is considered that the positional selectivity and reactivity of this ipso substitution are attributed to the leaving ability of substituent.

Experimental Section

VPC analyses were carried out with a Hitachi 163 gas chromatograph, using a 5% OV-1 column (2 m). ^{1}H NMR spectra were determined on a Hitachi R-600 spectrometer, using tetramethylsilane as internal standard. Mass spectra were recorded on a Hitachi RMU-6M instrument.

Reaction of 2,2′-Dipyridyl Sulfide (1) with Diphenyl Disulfide (2). Material 1 was prepared from 2-bromopyridine and potassium pyridinethiolate.[8] Material 2 and reference compound 2,2′-dipyridyl disulfide (5) were obtained commercially. A mixture of 1 (789.8 mg, 4.2 mmol) and 2 (913.1 mg, 4.2 mmol) was heated at 180 °C for 1 h in four sealed tubes. The resulting mixture was chromatographed on silica gel, eluting with chloroform to afford 1, 2, phenyl 2-pyridyl sulfide (3), phenyl 2-pyridyl disulfide (4), and 5. The products were identified by comparison of spectral data with those of the authentic samples. 3: δ_H ($CDCl_3$) 6.71–7.71 (8 H, m), 8.28–8.49 (1 H, m); ms, m/e 186 ($M^+ - H$). 4: δ_H ($CDCl_3$) 6.89–7.67 (8 H, m), 8.32–8.51 (1 H, m); ms, m/e 219 (M^+), 218 ($M^+ - H$), 186 ($M^+ - SH$). 5: δ_H ($CDCl_3$) 7.24–8.14 (6 H, m), 8.65–8.94 (2 H, m); ms, m/e 220 (M^+), 187 ($M^+ - SH$), 156 ($M^+ - 2S$).

Disproportionation Reaction between 2 and 5. Compound 4 was formed upon heating a mixture of 2 (365.6 mg, 1.6 mmol) and 5 (366.8 mg, 1.6 mmol) at 180 °C for 5 min in a sealed tube. When heating of this mixture was prolonged, 3 and phenyl pyridyl trisulfide, which was identified only by mass spectroscopy, were formed simultaneously. Phenyl pyridyl trisulfide: ms, m/e 250 ($M^+ - H$), 218 ($M^+ - SH$), 186 ($M^+ - SSH$), 154 ($M^+ - SSSH$), 141 ($M^+ - PhSH$), 109 ($M^+ - PhSSH$). Disulfide 4 (70.3 mg) was heated at 180 °C for 5 min in a sealed tube and analyzed directly by VPC. In this reaction, 2 and 5 were formed together with 4.

Reaction of 2 with 2-Pyridyl Tolyl Sulfide (6). Material 6 was prepared from 2-bromopyridine and potassium toluenethiolate.[8] A mixture of 6 (75.2 mg, 0.37 mmol) and 2 (80.3 mg, 0.37 mmol) was heated at 180 °C for 1 h in a sealed tube. Thus, phenyl tolyl disulfide (7), ditolyl disulfide (8), and 3 were identified by comparison of mass spectral degradation patterns with those of the authentic samples. 7: ms, m/e 232 (M^+), 123 ($M^+ - PhS$). 8: ms, m/e 246 (M^+), 123 ($M^+ - TolS$).

Disproportionation Reaction between 1 and 6,6′-Dimethyl-2,2′-thiodipyridine (12). Material 12 was obtained in a low yield by the reaction of 2-methyl-2′-bromopyridine and 2-methyl-2′-mercaptopyridine.[8] 2-Methyl-2′-bromopyridine was formed from 2-methyl-2′-aminopyridine and bromine.[9] 2-Methyl-2′-mercaptopyridine was formed from 2-methyl-2′-bromopyridine and thiourea.[10] A mixture of 1 (73.1 mg, 0.38 mmol) and 12 (82.3 mg, 0.38 mmol) was heated at 180 °C for 1 h in a sealed tube and analyzed directly by VPC. 6-Methyl-2,2′-thiodipyridine (13) was obtained together with 1 and 12. Retention time of 13 was intermediate between 1 and 12. The mass spectral peak was given at m/e 201 ($M^+ - H$).

Acknowledgment. The author thanks Prof. S. Oae, Okayama College of Science, for helpful support.

Registry No. 1, 4262-06-0; 2, 882-33-7; 3, 3111-54-4; 4, 24367-35-9; 5, 2127-03-9; 6, 95156-42-6; 7, 95156-44-8; 8, 61886-58-6; 12, 85060-42-0; 2-bromopyridine, 109-04-6; potassium pyridinethiolate, 79236-86-5; potassium toluenethiolate, 95156-43-7; 2-methyl-6-bromopyridine, 5315-25-3; 2-methyl-6-mercaptopyridine, 18368-57-5; 2-methyl-6-aminopyridine, 1824-81-3; thiourea, 62-56-6; 6-methyl-2,2′-thiodipyridine, 95193-22-9; phenyl pyridyl trisulfide, 95193-23-0.

(8) Campbell, J. R. *J. Org. Chem.* **1964**, *29*, 1830.
(9) Allen, C. F. H.; Thirtle, J. R. "Organic Syntheses"; Wiley: New York, 1955; Collect. Vol. 3, p 136.
(10) Phillips, M. A.; Shapiro, H. *J. Chem. Soc.* **1942**, 584.

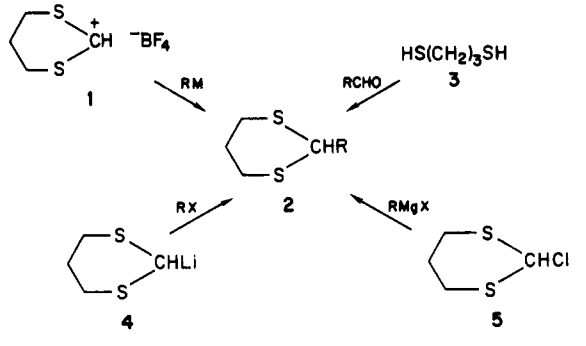
Reaction of Allylic Aluminum Reagents with 1,3-Dithienium Tetrafluoroborate and with 2-Chloro-1,3-dithiane: Preparation of 2-Substituted 1,3-Dithianes

Gérard Picotin and Philippe Miginiac*

Laboratoire de Chimie des Organométalliques, Université de Poitiers, 86022 Poitiers Cedex, France

Received October 11, 1984

1,3-Dithienium tetrafluoroborate (1) is readily prepared[1] from the reaction of 1,3-dithiane with trityl tetrafluoroborate. This easily handled and stable dithio carbocation is highly electrophilic: it reacts easily with trimethylsilyl enol ethers to give α-1,3-dithianyl ketones[2,3] and with allylic silanes to give 2-alken-2-yl-1,3-dithianes.[4] Therefore, it seemed reasonable that it should undergo reaction with organometallic reagents to give 2-substituted 1,3-dithianes 2. Up to now, most of the known dithianes 2 have been prepared either from the reaction of aldehydes with propane-1,3-dithiol (3)[5] or from the reaction of alkyl halides with 2-lithio-1,3-dithiane (4);[6] some of them have been obtained from Grignard reagents and 2-chloro-1,3-dithiane (5).[7]

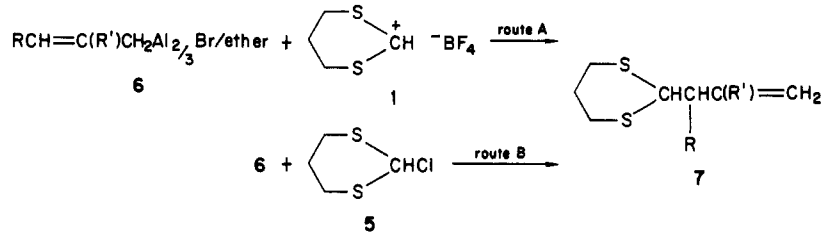


During the course of a study about the reactivity of 1,3-dithienium tetrafluoroborate (1) toward organometallic

(1) Corey, E. J.; Walinsky, S. W. *J. Am. Chem. Soc.* **1972**, *94*, 8932–8933.
(2) Paterson, I.; Price, L. G. *Tetrahedron Lett.* **1981**, *22*, 2829–2832.
(3) Paterson, I.; Price, L. G. *Tetrahedron Lett.* **1981**, *22*, 2833–2836.
(4) Westerland, C. *Tetrahedron Lett.* **1982**, *23*, 4835–4838.
(5) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231–237.
(6) Gröbel, B. T.; Seebach, D. *Synthesis* **1977**, 357–402, and references cited.
(7) Kruse, C. G.; Wijsman, A.; van der Gen, A. *J. Org. Chem.* **1979**, *44*, 1847–1851.

0022-3263/85/1950-1299$01.50/0

Table I



7	R	R′	yield,[a,b] % route A	yield,[a,b] % route B	bp, °C (torr)	n^{20}_D
a	H	H	87	61	71–72 (0.1)	1.5620
b	H	CH_3	71	53	78–79 (0.1)	1.5554
c	CH_3	H	74	53	75–76 (0.1)	1.5540
d	C_2H_5	H	71	50	76 (0.1)	1.5471
e	n-C_4H_9	H	78	55	91 (0.05)	1.5323
f	n-C_6H_{13}	H	75		133 (0.15)	1.5328

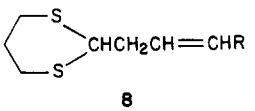
[a] Yield of isolated 7 with respect to the dithienium tetrafluoroborate (route A) and to the starting 2-chloro-1,3-dithiane (route B). [b] Satisfactory elemental analyses (±0.3% for C, H) were reported for all compounds.

reagents, we discovered that allylic aluminum reagents 6 react readily with 1 to give the expected 2-alken-2-yl-1,3-dithianes 7 (Table I, route A); moreover, when substituted allylic aluminum reagents 6 (R = alkyl, R′ = H) were used, the dithianes **7c–f**, which arise from an allylic rearrangement, are obtained free of any isomer.[8,9]

Similarly, the reaction of the aluminum derivative of 1-bromo-2-propyne gave 2-propyn-2-yl-1,3-dithiane (yield; 70%).

Next, in order to obtain the same dithianes 7, we considered the use of 2-chloro-1,3-dithiane (5); it has been shown that 5 reacts with aromatic, saturated, and vinylic Grignard reagents to give 2-substituted 1,3-dithianes 2.[7] Therefore, it appeared of interest to investigate the reaction of allylic aluminum reagents with this reactive halide; indeed, the dithianes 7 were obtained with a fair yield and this reaction proceeds with allylic rearrangement too (Table I, route B).[11]

Thus, it appears that the reaction of allylic aluminum reagents with either dithienium tetrafluoroborate or 2-chloro-1,3-dithiane is a way to 2-alken-2-yl-1,3-dithianes 7. This reaction is particularly valuable from substituted allylic aluminum reagents since it enables the preparation of dithianes **7c–f** which cannot be obtained through the alkylation of 2-lithio-1,3-dithiane (4) with the allylic halides $RCH{=}CHCH_2X$ since such a reaction, which proceeds mainly via a S_N2 mechanism,[12] would give the isomeric dithianes 8.



8

(8) The same type of 2-alken-2-yl-1,3-dithianes 7 has already been prepared from 1,3-dithienium tetrafluoroborate and allylic silanes;[4] yet, the use of allylic aluminum reagents avoids the preliminary preparation of allylic silanes.

(9) On the other hand, we observed that the reaction of 1 with either n-C_4H_9MgBr/ether or n-C_4H_9Li/hexane at −78 °C gives mainly 1,3-dithiane (3); this reaction involves most probably the elimination of a β-hydrogen atom from the organometallic compound. A similar elimination has already been observed when saturated organomagnesium and organolithium reagents were reacted with trityl tetrafluoroborate.[10]

(10) Reetz, M. T.; Stephan, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 44.

(11) We observed that the reaction of $CH_3CH{=}CHCH_2Al_{2/3}Br$/ether with the *gem*-halogenated ether n-$C_4H_9OCH_2Cl$ proceeds as well with rearrangement: the ether $CH_2{=}CHCH(CH_3)CH_2O$-n-C_4H_9 is the only product obtained (yield, 77%): bp 71–72 °C (60 torr); n^{20}_D 1.4141.

(12) Seebach, D. *Synthesis* **1969**, 17–36.

Experimental Section

General Procedure for Reaction of Allylic Aluminum Reagents with Dithienium Tetrafluoroborate. According to Gaudemar,[13] a pinch of $HgCl_2$ is added under nitrogen to a stirred suspension of aluminum (1.35 g, 0.05 mol) in ether (10 mL). The mixture is heated under reflux for 30 min. The heating is stopped and some pure allylic bromide $RCH{=}C(R')CH_2Br$ (5–10 drops) is rapidly added. As soon as the reaction starts (the ether boils again), a solution of the remaining bromide (total amount, 0.05 mol) in ether (30 mL) is slowly (6 h) added at such a rate that the mixture gently boils. When the addition is over, the mixture is heated under reflux for 1 h. The solution thus obtained is decanted off the excess aluminum into another flask which is next fitted with a bent tube containing dithienium tetrafluoroborate[1] (6.2 g, 0.03 mol). After cooling at −60 °C, under nitrogen, the salt is added (0.5 h) into the stirred solution. The temperature is allowed to reach slowly room temperature (3 h). The mixture is cooled to −90 °C and water (75 mL) is added. After 2 h of stirring at room temperature, the liquid mixture is decanted, the aqueous phase is extracted with ether (3 × 40 mL), and the combined organic phases are washed with NaOH (5 M) (3 × 40 mL) and water (4 × 50 mL). After drying (K_2CO_3), the dithiane 7 is distilled (Table I).

^1H NMR (CCl_4) **7a–f** 4.05 (t/**7a,b**, d/**7c–f**, J = 6 Hz, 1 H, CHS), 2.65–2.9 (m, 4 H, CH_2S); **7a,c–f** 4.8–6.2 (m, 3 H, $CH{=}CH_2$); **7b** 4.7–4.9 (m, 2 H, $=CH_2$), 2.75 (m, 3 H, CH_3); IR (neat) (cm^{-1}) 3080 (**7a–f**), 1650 (**7b**), 1640 (**7a,c–f**), 1460 (**7c–f**), 1420, 1275, 1245, 1180 (**7a–f**), 990 (**7a,c–f**); the 905-cm^{-1} absorption, characteristic of the dithiane system,[12,14] appears together with either the 910-cm^{-1} absorption (**7a,c–f**) or the 890-cm^{-1} absorption (**7b**).

2-Propyn-2-yl-1,3-dithiane was prepared according to the above procedure from the aluminum derivative of 1-bromo-2-propyne prepared in ether:[15] bp 73 °C (0.1 torr); n^{20}_D 1.5812; ^1H NMR (CCl_4) 4.1 (t, J = 7 Hz, 1 H, CHS), 2.5–3 (m/dd, 6 H, $CH_2C{\equiv}$, CH_2S); IR (neat) (cm^{-1}) 3280, 2130, 1470, 1275, 1245, 1180, 907.

General Procedure for Reaction of Allylic Aluminum Reagents with 2-Chloro-1,3-dithiane. According to Akai and Oki,[16] *N*-chlorosuccinimide (14 g, 0.105 mol) was added over a 1-h period to a solution of 1,3-dithiane (7.2 g, 0.06 mol) in benzene (150 mL). The temperature of the reaction was maintained at 20–25 °C by intermittent external cooling. The mixture was next stirred magnetically for 1 h and rapidly filtered under nitrogen through a sintered filter funnel into a pressure equalizing addition funnel to give a clear, bright yellow solution which rapidly became turbid. This solution was immediately added, under nitrogen and over a 1-h period, to the aluminum reagent, maintained at −60

(13) Gaudemar, M. *Bull. Soc. Chim. Fr.* **1958**, 1475–1477.

(14) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553–3560.

(15) Gaudemar, M. *Ann. Chim. Fr.* **1956** (13), *1*, 161–213.

(16) Arai, K.; Oki, M. *Tetrahedron Lett.* **1975**, 2183–2186.

°C, prepared[13] from RCH=C(R')CH_2Br (0.17 mol), aluminum (4.6 g, 0.17 mol), and ether (110 mL) previously decanted off the excess aluminum. The resultant mixture was allowed to reach slowly room temperature (3 h) and was then poured onto a mixture of ice–water. The aqueous layer was extracted with ether (3 × 75 mL) and the combined organic layers were washed with NaOH (5 M) (3 × 50 mL) and water (4 × 70 mL). After drying (K_2CO_3), the dithiane 7 was distilled at once.

Registry No. 1, 39915-66-7; **5**, 57529-04-1; **6a**, 67702-85-6; **6b**, 70688-45-8; **6c**, 12354-30-2; **6d**, 70688-43-6; **6e**, 70688-44-7; **6f**, 95313-92-1; **7a**, 63382-29-6; **7b**, 69178-01-4; **7c**, 95313-87-4; **7d**, 95313-88-5; **7e**, 95313-89-6; **7f**, 95313-90-9; aluminum, 7429-90-5; 1,3-dithiane, 505-23-7; propargyl bromide, 106-96-7; allyl bromide, 106-95-6; methallyl bromide, 1458-98-6; crotyl bromide, 4784-77-4; 2-pentenyl bromide, 20599-27-3; 2-heptenyl bromide, 34686-77-6; 2-nonenyl bromide, 76853-14-0; $(HC{\equiv}C\text{-}CH_2)_3Al_2Br_3$, 61781-91-7; $HC{\equiv}C\text{-}CH_2\overline{CSCCCS}$, 95313-91-0.

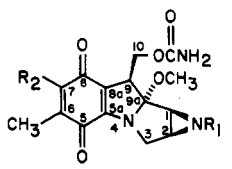
Stereochemical Relationship between Mitomycins A, B, and C

Ulfert Hornemann* and Michael J. Heins

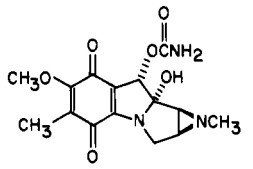
School of Pharmacy, University of Wisconsin, Madison, Wisconsin 53706, and Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy, Purdue University, West Lafayette, Indiana 47906

Received August 8, 1984

As a consequence of the recent high precision determination of the absolute configuration of mitomycin C (Ic) as C_1 (*S*), C_2 (*S*), C_9 (*S*), C_{9a} (*R*) by X-ray crystallographic analysis,[1] there now exists uncertainty about the stereochemical and perhaps even the biosynthetic relationships among some of the naturally occurring mitomycins.[2] This situation prompts us to report on studies which show that mitomycin A (Ia) and mitomycin B (II) have the same absolute configuration at C_1 and C_2. This result supports the suggestion that all naturally occurring mitomycins are the products of one main biosynthetic pathway differing only in late stages for individual members and are not the end products of two similar but early divergent biosynthetic pathways.



Ia MITOMYCIN A
R_1=H, R_2=OCH_3

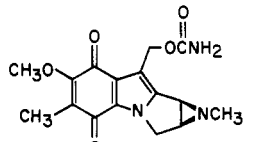


II MITOMYCIN B

Ib N-METHYLMITOMYCIN A
R_1=CH_3, R_2=OCH_3

Ic MITOMYCIN C
R_1=H, R_2=NH_2

Id PORFIROMYCIN
R_1=CH_3, R_2=NH_2



III 7-METHOXY-1,2-(N-METHYLAZIRIDINO) MITOSENE

In several fermentations of *Streptomyces* species[2] including *S. caespitosus*,[3] mitomycin A is often produced in greatest abundance followed by mitomycins B and C, and porfiromycin (Id). Under different fermentation conditions, the clinically useful mitomycin C[4,5] is the most abundant compound in *S. caespitosus*, suggesting a close biosynthetic relationship between mitomycins A and C. Mitomycin A has been converted into mitomycin C by treatment with ammonia.[6,7] The product was identical with mitomycin C by paper chromatography, IR, UV, and X-ray powder diffraction. Mitomycin C can be converted into porfiromycin by methylation, and the latter has been converted into *N*-methylmitomycin A (Ic), which occurs naturally[8] and which can also be readily obtained from mitomycin A by methylation.[2] However, chemical conversions of mitomycin A and C, porfiromycin, and *N*-methylmitomycin A into mitomycin B, or vice versa, have never been reported.

With respect to their biosynthesis,[2] it is known that these antibiotics are formed from an early intermediate of the shikimic acid pathway which provides the benzoquinone moiety and from D-glucosamine which appears to contribute label to C_1, C_2, C_3, C_{9a}, C_9, and C_{10} as well as the nitrogen atom of the aziridine ring. L-Glucosamine is not a mitomycin precursor and D-galactosamine and D-mannosamine which are two epimers of D-glucosamine are less efficiently incorporated than D-glucosamine. The incorporation of D-[1-^{13}C,^{15}N]glucosamine into mitomycin B occurs essentially without separation of the two labeled atoms. All precursors tested appear to label mitomycins A and B in a constant ratio commensurate with the concentration ratio of these antibiotics in the fermentation broth.

The absolute configurations of mitomycins A and B have been reported on the basis of low precision X-ray crystallographic results as C_1 (*R*), C_2 (*R*), C_9 (*R*), C_{9a} (*S*),[9,10] and as C_1 (*R*), C_2 (*R*), C_9 (*S*), C_{9a} (*S*),[11,12] respectively. If these assignments are correct, the results of the biosynthetic studies make it necessary to postulate the occurrence of an inversion of the chirality of C_2 of D-glucosamine without cleavage of the C_2–N bond during mitomycin biosynthesis.[2] This situation prompted Shirahata and Hirayama to determine the absolute configuration of mitomycin C by X-ray crystallographic analysis. These authors have obtained the best precision of any of the published X-ray determinations of mitomycins and have established the absolute configuration of mitomycin C with high probability. Their results given above make it very likely that mitomycin A also has the same chirality at its four asym-

(1) Shirahata, K.; Hirayama, N. *J. Am. Chem. Soc.* **1983**, *105*, 7199–7200.
(2) Hornemann, U. *Antibiotics (N.Y.)* **1981**, *4*, 295–312.
(3) Wakaki, S.; Marumo, H.; Tomioka, K.; Shimizu, G.; Kato, E.; Kamada, H.; Kudo, S.; Fujimoto, Y. *Antibiot. Chemother. (Washington, D.C.)* **1958**, *8*, 228.
(4) Carter, S. K.; Crooke, S. T. "Mitomycin C–Current Status and New Developments"; Academic Press: New York, 1979.
(5) Perez, D. J.; Powles, T. J.; Gazet, J. C.; Ford, H. T.; Coombes, R. C. *Cancer Chemother. Pharmacol.* **1984**, *13*, 36–38.
(6) Lefemine, D. V.; Dann, M.; Barbatschi, F.; Hausmann, W. K.; Zbinovsky, V.; Monnikendam, P.; Adam, J.; Bohonos, N. *J. Am. Chem. Soc.* **1962**, *84*, 3184–3185.
(7) Uzu, K.; Harada, Y.; Wakaki, S. *Agric. Biol. Chem.* **1964**, *28*, 388–393.
(8) Kasai, M.; Shirahata, K. (Kyowa Hakko), Japan Kokai 80 45 322, March 31, 1980.
(9) Tulinsky, A. *J. Am. Chem. Soc.* **1962**, *84*, 3188–3190.
(10) Tulinsky, A.; van Den Hende, J. H. *J. Am. Chem. Soc.* **1967**, *89*, 2905–2911.
(11) Yahashi, R.; Matsubara, I. *J. Antibiot.* **1976**, *29*, 104–106.
(12) Correction notice published in *J. Antibiot.* **1978**, *31*, last page.

0022-3263/85/1950-1301$01.50/0