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Regioselective addition of aldimines to the 2-propenyl-1,3-dithiane anion

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Abstract

The allyllithium generated from 2-propenyl-1,3-dithiane reacts exclusively at the y-site with aldimines, but the BF_3-mediated reaction with aliphatic aldimines occurs predominantly at the a-site.

Introduction

Although the reactions of heteroatom-substituted allylic organometallic compounds have been extensively studied [1–3], the controlling factors of regiochemistry are not fully understood. We and others have found that the regioselectivity in the reaction of an unsymmetric allylic organometallic compound is dependent on several factors, such as the attacking electrophile [4,5], the additive of hexamethylphosphoramide [6,7], and the complexation with Lewis acids [8,9]. So far, related reactions with alkyl halides and carbonyl compounds have been intensely investigated, but the corresponding reaction with imines is rarely examined [10–12]. In continuation of the study on dithio-substituted allylic organometallic compounds, we now report that regioselectivity for the allyllithium **1** in reaction with aldimines can be manipulated by mediation of BF_3.

Results and discussion

As shown in Table 1, the crotyllithium generated from 2-propenyl-1,3-dithiane in THF solution [13] reacts exclusively at the y-site with aldimines. On the other hand, a-addition occurs predominantly when the ethereal crotyllithium solution is treated with BF_3 before the addition of the imine (prepared from butylamine and an aliphatic aldehyde [14]). The α-selectivity is retained when a mixed ethereal solution of propylidene butylamine and BF_3 is added to the crotyllithium **1**, to give exclusively the a-adduct 3. THF should not be used as solvent in the presence of BF_3 because undergoes a ring-opening reaction [15]. As we previously proposed, the a-site in the crotyllithium **1** is harder than the y-site, so the regioselectivity is best

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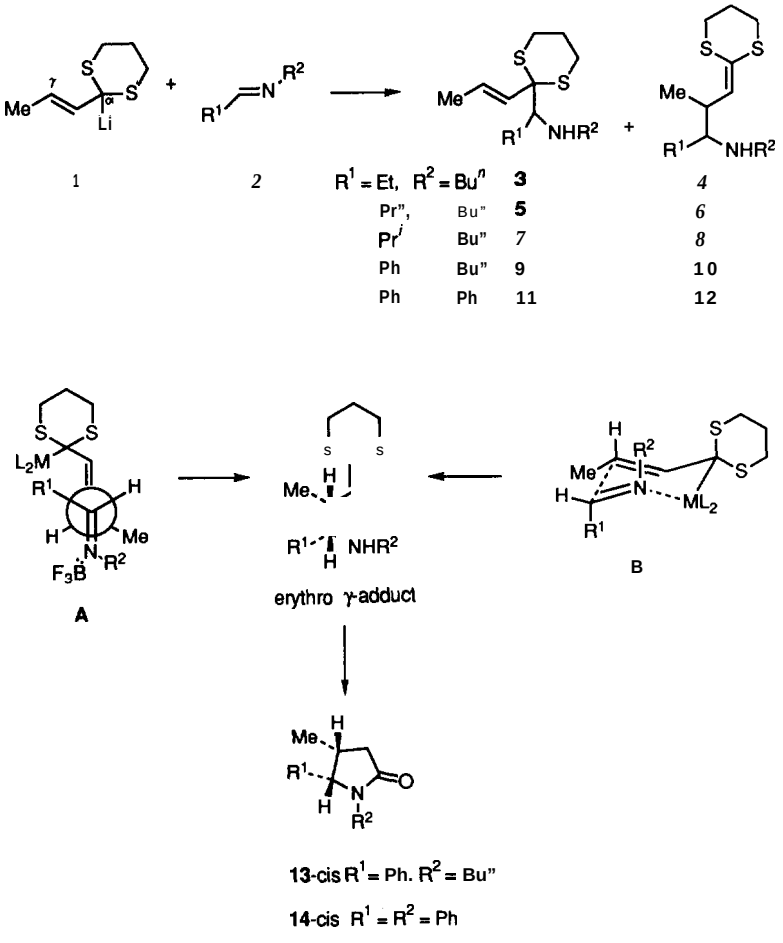
Table 1

Addition reactions of imines with the crotyllithium 1

Entry	Imine	solvent	BF_3 (equiv.)	Products (yield, %)
1	EtCH=NBu^n	THF	0	4 (73) [a]
2	EtCH=NBu^n	Et_2O	1	3 (90) [b]
3	Pr^{n}CH=NBu^n	THF	0	6 (74) [a]
4	Pr^{n}CH=NBu^n	Et_2O	1	5 (64) + 6 (4)
5	Pr^{i}CH=NBu^n	THF	0	8 (60) [a,c]
6	Pr^{i}CH=NBu^n	Et_2O	1	7 (72) + 8 (5)
7	PhCH=NBu^n	THF	0	10 (35) [a]
8	PhCH=NBu^n	Et_2O	1	9 (36) + 10 (54) [d]
9	PhCH=NPh	THF	0	12 (93) [a]
10	PhCH=NPh	Et_2O	1	11 (17) + 12 (55) [e]

[a] The product was obtained as a diasterwmeric mixture. *4-erythro/4-threo = 66 : 34, 6-erythro/6-threo = 69 : 31,* *8-erythro/8-threo* = 60 : 40, *10-erythro/10-threo* = 15 : 85, *12-erythro/12-threo = 42 : 58.* [b] Either addition of the aldimine to the crotyllithium/BF_3 mixture or addition of the aldimine/BF_3 mixture to the crotyllithium give the single product 3. [c] The reaction was warmed to room temperature for 1 h before quenching by NH_4Cl. No addition product formed at −78 °C. [d] Either addition mode, as described in entry 2, yields products of similar composition, viz., 9 and 10 (*erythro/threo = 67 : 33).* [e] *12-erythro/12-threo = 94 : 6.*



Scheme 1.

accounted for by the hard and soft acid and base principle [5,16]. Accordingly, the relatively soft electrophile of aliphatic aldimine prefers reaction at the y-site. However, the imine would become much harder when coordinated with BF_3. Thus, with BF_3 reaction at the hard a-site was realized. Owing to the delocalizing effect of the phenyl group, an increase in hardness would be less profound in the complex of a benzaldehyde imine and BF_3; this is reflected in reactions (entries 8 and 10) which both give a- and y-addition products.

The y-addition reaction of allyllithium 1 with the complex of imine-BF_3 probably involves the acyclic transition state A (Scheme 1). The antiperiplanar mode of reaction can account for the *erythro* selectivity of y-addition products [11,17], i.e. **10**-*erythro*/**10**-*threo* = 2/1 and **12**-*erythro*/**12**-*threo* = 1.5/1 (entries 8 and 10). The respective diastereomers of 10 and 12 were subsequently treated with trifluoroacetic acid and *N*-bromosuccimide to give y-lactams 13 and 14 [18,19]. The P-methyls of 13-h and **14**-*cis* compounds appeared at unusually high fields of δ 0.62 and δ 0.72 in NMR spectra owing to the shielding effect by the adjacent phenyl group [5,11]. When allyllithium 1 was pretreated with BF_3, the possibility of it behaving as an allylboron [8] or as an "ate" complex [20] cannot be excluded. However, the *erythro* selectivity of its y-reaction with aldimines may deduced from either transition state, A or B (M is boron). The y-additions in entries 1, 3, 5 also show that *erythro* isomers are preferentially formed (*erythro*/*threo* = 1.5 to 2.2). These reactions probably proceed via the chair-like cyclic transition state B (M is lithium), in which lithium coordinates with the nitrogen atom *syn* to the R^1 group [11]. Abnormal *threo* selectivity for benzaldehyde imines in the reactions, entries 7 and 9 (*erythro*/*threo* = 0.18 and 0.72) was observed as reported previously [11], although the nature of transition state is unclear.

Use of dithiane as an umpolung of carbonyl group is well documented [21]. Our present method furnishes the dithianes containing additional functional groups (amino and double bond) suitable for further elaboration in many aspects.

Experimental

Elemental analyses were carried out with a Perkin-Elmer 240c elemental analyzer. Infrared spectra were recorded on a Perkin-Elmer 985 infrared spectrophotometer. The nuclear magnetic resonance spectra were recorded on a Bruker AM-300WB or AC-200 spectrometer. Mass spectra were recorded on a Finnigan TSQ 46c spectrometer operating at an ionizing voltage of 70 eV. Merck silica gel 60 F sheets were used for the analytical thin-layer chromatography. Reaction products were separated by flash chromatography by elution with a gradient of *n*-hexane/EtOAc/Et_3N. Further purification was carried out by a Waters Association M45 high-pressure chromatograph on a μ-Porasil column (0.78 cm *X* 25 cm).

General procedure for the addition reaction of I to aldimines. A solution of 0.8 ml of *n*-BuLi (1.6 M in hexane) under N_2 was added dropwise to a solution of 2-propenyl-1,3-dithiane (160 mg, 1.0 mmol) in THF (0.5 ml) at $-30°C$. The mixture was stirred for 20 min, cooled to $-78°C$, and the appropriate aldimine (1.0 mmol) was added. After l-2 h at $-78°C$, a saturated NH_4Cl solution was added, and the mixture was taken up with EtOAc. Separation and analysis of the products from organic phase were achieved by chromatographic and spectroscopic methods.

In case of BF_3-mediated reactions, diethyl ether (5 ml) was used as solvent and freshly distilled $BF_3 \cdot Et_2O$ (1 equiv.) was added prior to the addition of aldimines.

a-Addition product 3 from 1 and propylidene butylamine. Pale yellow oil, R_f 0.4 (5% EtOAc in hexane). δ_H ($CHCl_3$) 0.75-1.10 (6 H, m), 1.12-1.60 (6 H, m), 1.78 (3 H, d, J = 6 Hz), 1.70-2.10 (3 H, m), 2.42-3.02 (7 H, m), 5.48 (1 H, br d, J = 16 Hz), 5.68-6.15 (1 H, m). ν_{max} (neat) 3337, 3015, 2921, 1451, 1419, 1374, 1113, 974 cm-'. *m/z (W) 274* (11, $M^+ + 1$), 243 (10), 201 (10), 159 (26), 114 (100), 85 (65). Anal. Calcd for $C_{14}H_{27}NS_2$: C, 61.48; H, 9.95; N, 5.12. Found: C, 61.38; H, 10.15; N, 4.86.

y-Addition products 4 from 1 and propylidene butylamine. Mixture of *erythro* and *threo* isomers (66 :34), R_f 0.17 (8% EtOAc in hexane containing 0.5% Et_3N). δ_H (CDCl,) 0.82 (6 H, t, J= 7.5 Hz), 0.89 (2.0 H, d, J= 7.2 Hz, R_2CHCH_3, *erythro*)/0.88 (1.0 H, d, J= 7.2 Hz, *threo*), 1.14-1.39 (6 H, m), 2.05-2.11 (2 H, m), 2.16–2.20 (1 H, m, NH), 2.44-2.52 (2 H, m, NCH,), 2.73-2.88 (6 H, m), 5.75 (0.66 H, d, J = 10 Hz)/5.77 (0.34 H, d, J = 10 Hz). ν_{max} (neat) 3349, 2955, 2926, 1451, 1110, 880 cm-'. *m/z* (%) 274 (7, $M^+ + 1$), 114 (100). Anal. Calcd for $C_{14}H_{27}NS_2$: C, 61.48; H, 9.95; N, 5.12. Found: C, 61.30; H, 9.73; N, 5.04.

a-Addition product 5 from I and butylidene butylamine. Pale yellow oil, R_f 0.28 (5% EtOAc in hexane). δ_H (CDCl,) 0.80-1.05 (6 H, m), 1.10-1.70 (8 H, m), 1.81 (3 H, d, J = 6 Hz), 1.72-2.10 (3 H, m), 2.20-3.20 (7 H, m), 5.50 (1 H, br d, J = 15 Hz), 6.00 (1 H, m). ν_{max} (neat) 3334, 3050, 2957, 1457, 1374, 1275, 974 cm-'. *m/z* (%) 288 (1, $M^+ + 1$), 182 (75), 159 (12), 128 (100). Anal, Calcd for $C_{15}H_{29}NS_2$: C, 62.66; H, 10.17; N, 4.87. Found: C, 62.34; H, 10.41; N, 4.76.

y-Addition products 6 from I and butylidene butylamine. Mixture of *etythro* and *threo* isomers (70: 30), R_f 0.17 (8% EtOAc in hexane containing 0.5% Et_3N). δ_H (CDCl,) 0.85 (6 H, t, J = 7 Hz), 0.93 (2.1 H, d, J = 6.6 Hz, *erythro*)/0.92 (0.9 H, d, J= 6.6 Hz, *threo*), 1.18-1.43 (8 H, m), 2.08-2.16 (2 H, m), 2.29-2.32 (1 H, m), 2.49-2.59 (2 H, m), 2.78-2.91 (6 H, m), 5.82 (0.7 H, d, J = 9.6 Hz)/5.83 (0.3 H, d, J = 9.6 Hz). ν_{max} (neat) 3370, 2955, 2926, 1457, 1110 cm-'. *m/z (W) 288 (4,* $M^+ + 1$), 128 (100). Anal. Calcd for $C_{15}H_{29}NS_2$: C, 62.66; H, 10.17; N, 4.87. Found: C, 62.68; H, 10.07; N, 4.79.

a-Addition product 7 from I and isopropylidene butylamine. Pale yellow oil, R_f 0.37 (5% EtOAc in hexane). δ_H (CDCl,) 0.80-1.10 (9 H, m), 1.12-1.60 (5 H, m), 1.76 (3 H, d, J = 6 Hz), 1.70-2.38 (3 H, m), 2.42-3.00 (7 H, m), 5.45 (1 H, br d, J = 15 Hz), 5.90 (1 H, m). ν_{max} (neat) 3333, 3015, 2953, 1457, 1419, 1374, 1113, 975 cm^{-1}. *m/z%) 288 (1,* $M^+ + 1$), 243 (11), 159 (3), 128 (100). Anal. Calcd for $C_{15}H_{29}NS_2$: C, 62.66; H, 10.17; N, 4.87. Found: C, 62.29; H, 10.17; N, 4.82.

Y-Addition products 8 from 1 and isobutylidene butylamine. Mixture of *erythro* and *threo* isomers (60 :40), R_f 0.1 (5% EtOAc in hexane). δ_H (CDCl,) 0.70-1.00 (12 H, m), 1.12-1.50 (5 H, m), 1.72-2.38 (3 H, m), 2.40–2.92 (8 H, m), 5.80 (0.6 H, d, J = 10 Hz, *erythro*)/5.90 (0.4 H, d, J = 10 Hz, *threo*), ν_{max} (neat) 3490, 2954, 1580, 1457, 1419, 1109, 911 cm-'. *m/z* (%) 288 (75, $M^+ + 1$), 128 (100).

a-Addition product 9 from I and benzylidene butylamine. R_f 0.28 (5% EtOAc in hexane). δ_H (CDCl,) 0.80 (3 H, t, J = 6 Hz), 1.00-1.56 (4 H, m), 1.78 (3 H, d, J= 6 Hz), 1.72-2.10 (3 H, m), 2.39 (2 H, t, J= 7 Hz), 2.50-2.95 (4 H, m), 3.85 (1 H, s), 5.40 (1 H, br d, J= 16 Hz), 5.62-6.00 (1 H, m), 7.20-7.35 (5 H, m). ν_{max} (neat) 3315, 3058, 2915, 1597, 1489, 1448, 1374, 755, 702 cm^{-1}. m/z (%) 322 (35,

$M^+ + 1$), 249 (23), 162 (100). Anal. Calcd for $C_{18}H_{27}NS_2$: C, 67.24; H, 8.46; N, 4.36. Found: C, 66.90; H, 8.70; N, 4.18.

y-Addition products 10 from I and benzylidene butylamine. Mixture of erythro and *threo* isomers (15 : 85), R_f 0.11 (5% EtOAc in hexane). δ_H 0.92 (0.45 H, d, J = 7 Hz, *erythro*)/0.64 (2.55 H, d, J = 7 Hz, *threo*), 0.82 (3 H, t, J = 7 Hz), 1.18-1.39 (4 H, m), 1.74-1.79 (1 H, m), 2.00-2.14 (2 H, m), 2.28-2.43 (2 H, m), 2.54-3.07 (5 H, m), 3.50 (0.15 H, d, J = 6 Hz)/3.28 (0.85 H, d, J = 8 Hz), 5.71 (0.15 H, d, J = 10 Hz)/5.77 (0.85 H, d, J = 10 Hz), 7.10-7.31 (5 H, m). ν_{max} (neat) 3323, 3079, 2923, 1598, 1488, 762, 702 cm^{-1}. *m/z* (W) 322 (30, $M^+ + 1$), 162 (100). Anal. Calcd for $C_{18}H_{27}NS_2$: C, 67.24; H, 8.46; N, 4.36. Found: C, 67.58; H, 8.25; N, 4.04.

a-Addition product II from I and benzylidene benzenamine. R_f 0.22 (1% EtOAc in hexane). δ_H ($CDCl_3$) 1.80 (3 H, d, J = 7 Hz), 1.70-2.30 (2 H, m), 2.40–3.30 (4 H, m), 4.48 (1 H, m), 4.83 (1 H, m), 5.35 (1 H, br d, J= 15 Hz), 5.92 (1 H, m), 6.42-6.70 (3 H, m), 6.91–7.08 (2 H, m), 7.20-7.60 (5 H, m). ν_{max} (neat) 3395, 3022, 2909, 1598, 1498, 1448, 1314, 749, 701 cm-'. m/z (W) 341 (16, M^+), 266 (41), 182 (100), 159 (70). Anal. Calcd for $C_{20}H_{23}NS_2$: C, 70.34; H, 6.79; N, 4.10. Found: C, 69.98; H, 6.95; N, 3.95.

y-Addition products I2 from I and benzylidene benzenamine. Mixture of *erythro* and *threo* isomers (40 : 60), R_f 0.08 (1% EtOAc in hexane). δ_H ($CDCl_3$) 0.98 (1.2 H, d, J = 7.5 Hz, *erythro*)/0.89 (1.8 Hz, d, J= 7.5 Hz, *threo*), 1.90-2.25 (2 H, m), 2.68-3.38 (5 H, m), 4.17 (1 H, br s, NH), 4.26 (0.4 H, d, J = 4.5 Hz)/3.92 (0.6 H, d, J = 8 Hz), 5.79 (0.4 H, d, J = 10 Hz)/5.90 (0.6 H, d, J = 10 Hz), 6.27-6.55 (3 H, m), 6.80-7.00 (2 H, m), 7.10–7.40 (5 H, m). ν_{max} (neat) 3397, 3021, 2958, 2925, 1597, 1498, 868, 749, 701 cm-'. *m/z* (W) 342 (2, $M^+ + 1$), 182 (100). Anal. Calcd for $C_{20}H_{23}NS_2$: C, 70.34; H, 6.79; N, 4.10. Found: C, 69.96; H, 7.05; N, 4.07.

General procedure for hydrolysis of y-addition products 10 and 12 to give lactams 13 and 14. A solution of the y-addition product (0.4 mmol) in CH_2Cl_2 (8 mL) was treated with CF_3CO_2H (0.48 mmol in 1 mL of CH_2Cl_2) at room temperature for 30 min. After the solvent was removed, the reddish residue was taken up with EtOAc (10 mL) and treated with a small amount of Na_2CO_3. The mixture was filtered through a short column of silica gel. The concentrated filtrate, showing no NMR resonance for olefinic proton, was dissolved in 5 mL of CH_3CN. A solution (2 mL, H_2O/CH_3CN = 4 : 1) of *N*-bromosuccinimide (2.4 mmol) was added, and the mixture was stirred at room temperature for 15 min. After addition of saturated Na_2CO_3, the mixture was extracted with $CHCl_3$/*n*-hexane (1: 1). The organic phase was thoroughly washed with saturated Na_2CO_3 (6-8 times), dried with anhydrous Na_2SO_4, concentrated and separated by chromatography to give the desired lactam in 43-60% yield. 13-*cis*: δ_H 0.60 (3 H, d, J = 7.0 Hz), 0.83 (3 H, t, J = 7.3 Hz), 1.14-1.44 (4 H, m), 2.14-2.48 (2 H, m), 2.51-3.76 (3 H, m), 4.58 (1 H, d, J = 8.2 Hz), 7.00-7.03 (2 H, m), 7.20-7.36 (3 H, m). ν_{max} (neat) 2957, 1687, 1600, 1452, 805 cm-'. *m/z* (%) 231 (M^+, 32), 216 (5), 188 (83), 91 (100). 13-*trans*: δ_H 0.79 (3 H, t, J = 7.1 Hz), 1.09 (3 H, d, J = 6.5 Hz), 1.14-1.44 (4 H, m), 2.14-2.46 (2 H, m), 2.50-3.75 (3 H, m), 4.06 (1 H, d, J= 5.9 Hz), 7.14-7.16 (2 H, m), 7.20-7.36 (3 H, m). ν_{max} 3029, 2963, 1697, 1584, 1489, 876, 748, 702 cm^{-1}. Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.62; H, 9.13; N, 6.24. 14-*cis*: δ_H 0.72 (3 H, d, J = 6.8 Hz), 2.40 (1 H, dd, J = 16.7, 11.5 Hz), 2.65 (1 H, dd, J = 16.7, 8.0 Hz), 2.76-2.91 (1 H, m), 5.12 (1 H, d, J= 7.8 Hz), 7.10-7.15 (2 H, m), 7.26-7.44 (8 H, m). Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82, N, 5.57. Found: C, 80.95;

H, 6.88; N, 5.32. 14-*trans*: δ_H 1.24 (3 H, d, *J* = 6.4 Hz), 2.26-2.45 (2 H, m), 2.88-2.95 (1 H, m), 4.68 (1 H, d, *J* = 5.6 Hz). 7.10-7.15 (2 H, m), 7.26-7.44 (8 H, m).

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