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REACTION OF TRIALKYLBORANES WITH 2-BROMO-6-LITHIOPYRIDINE

STEREOSPECIFIC ALKYLATIVE CLEAVAGE OF PYRIDINE RING[1]

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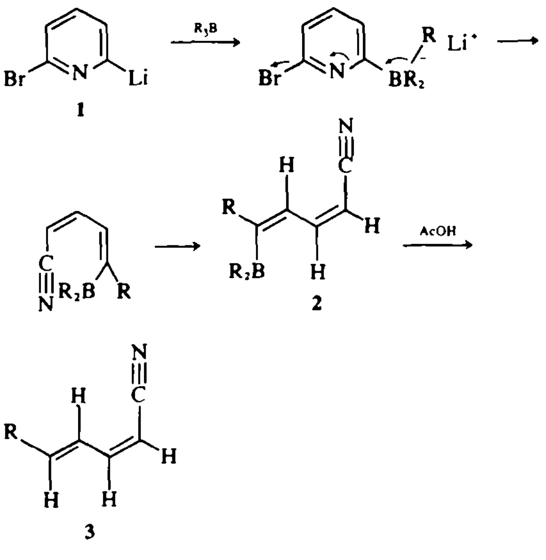
Abstract—Reaction of 2-bromo-6-lithiopyridine with trialkylboranes affords 5-alkyl-5-dialkylboryl-2(*Z*), 4(*E*)-pentadienenitriles by stereospecific alkylative cleavage of the pyridine ring. These intermediary vinylboranes are versatile reagents for the preparation of 5-alkyl-2(*Z*), 4(*E*)-pentadienenitriles, 5,5-dialkyl-4-pentenenitriles and 5,5-dialkyl-2,4-pentadienenitriles.

Recent progress of organoboron chemistry has disclosed several useful reactions for stereospecific olefin synthesis.[2] Dienes[3] as well as α,β-olefinic esters[4] with rigorous stereochemistry have been prepared from the corresponding acetylenic compounds by reductive alkylation via vinylboranes. This paper describes a stereospecific alkylative cleavage of pyridine ring by trialkylboranes: high yield formation of 5-alkyl-5-dialkylboryl-2(*Z*),4(*E*)-pentadienenitriles (**2**) from 2-bromo-6-lithiopyridine (**1**)[5] and trialkylboranes. Furthermore it refers to subsequent transformations of **2** to 5-alkyl-2(*Z*),4(*E*)-pentadienenitriles (**3**) in a stereospecific way, to 5,5-dialkyl-4-pentenenitriles (**4**) and finally 5,5-dialkyl-2(*Z*),4-pentadienenitriles (**6**), respectively. This operationally simple and stereospecific procedure is a novel addition to the rapidly growing group of syntheses with organoboranes, to the unsaturated nitrile synthesis,[6] and to the cleavage reactions of the very stable heteroaromatic ring.[7]

Reaction of tripropylborane with 2-bromo-6-lithiopyridine (**1**) in ether-hexane solvent afforded 5-propyl-5-dipropylboryl-2(*Z*),4(*E*)-pentadienenitrile (**2**, R = n-Pr) which was not isolated in pure state but spectrometrically detected.[8] Successive treatment of the reaction mixture with glacial acetic acid gave 2(*Z*),4(*E*)-octadienenitrile (**3**, R = n-Pr) in 80% overall yield. The homogeneity of the diene-nitrile was ascertained by GLC and also by Eu(fod)$_3$-shifted NMR which established the stereochemistry of the dienenitrile at the same time.[9] Tributyl- and triisopropylborane afforded 2(*Z*),4(*E*)-nonadienenitrile [**3**, R = (CH$_2$)$_3$CH$_3$, 93% overall yield] and 6-methyl-2(*Z*),4(*E*)-heptadienenitrile [**3**, R = (CH$_3$)$_2$CH, 60% overall yield], respectively.

The alkylative cleavage of the pyridine ring is explained by assuming the following steps: (1) trialkylborane reacts with 2-bromo-6-lithiopyridine to give lithium (6-bromo-2-pyridyl)trialkylborate;[10] (2) alkyl shift from boron to carbon occurs with inversion of the configuration at the olefinic carbon; (3) concertedly with (2) cleavage of C–N bond and elimination of bromide ion proceed. Stereochemistry at the migrating carbon could not be discussed from the above described results but retention of configuration was presumed by the analogy to the reported reaction of alkenylborates.[11] Orbital consideration[12] indicated that this concerted alkyl shift, ring cleavage and bromide elimination process is a symmetrically allowed $[{}_{\sigma}2_{s} + {}_{\sigma}2_{s} + {}_{\pi}2_{s}]$ process.[13]

Further synthetic utility of the intermediary vinylboranes **2** has been shown by transformation either to 5,5-dialkyl-4-pentenenitrile (**4**) or to 5,5-dialkyl-2(*Z*), 4-pentadienenitrile (**6**), respectively.



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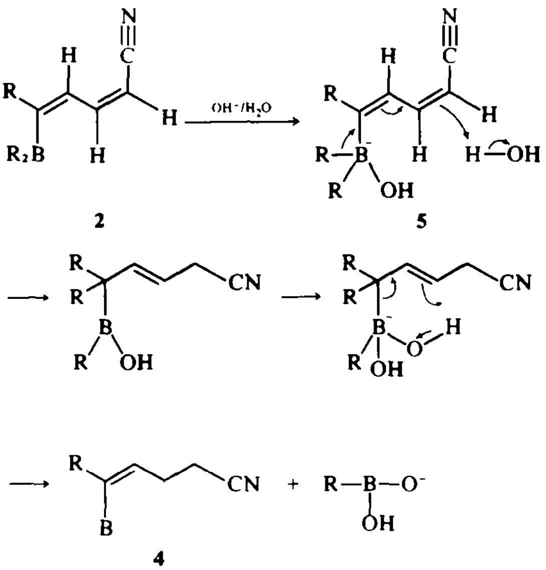
Treatment of the reaction mixture containing 5-dipropylboryl-2(*Z*),4(*E*)-octadienenitrile (**2**, R = n-Pr) with aqueous alkali afforded 5-propyl-4-octenenitrile (**4**, R = n-Pr) in 94% overall yield, no isomeric product being detected. Analogous procedure with tributylborane or triisopropylborane afforded 5-butyl-4-nonenenitrile and 5-isopropyl-6-methyl-4-heptenenitrile, respectively.

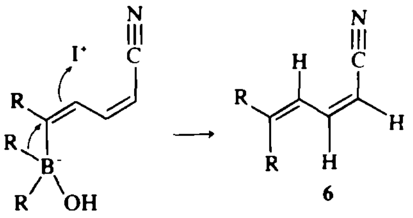
The following scheme should explain this transformation. Hydroxyl anion attack on boron affords the borate **5**, in which alkyl migration from boron to carbon gives a nitrile-stabilized carbanion. The protonated intermediate is hydrolyzed to give 5,5-dialkyl-4-pentenenitrile **4**. An analogous mechanism has been supposed by Brown and Nambu in the preparation of β,γ-unsaturated esters from γ-dialkylboryl-α,β-unsaturated esters.[14]

The above described 5-propyl-4-octenenitrile (**4**, R = n-Pr) was reduced into 5-propyl-4-octenal in 62% yield by treatment with diisobutyl-aluminium hydride.[15] Propylure was prepared from this aldehyde by Meyers and Collington[16] in 64% yield. Combination with the reported



procedure gave propylure in 37% overall yield based on dibromopyridine.

In contrast to the ene-nitrile formation, treatment with aqueous alkali and iodine gave a mixture of 5,5-dialkyl-2(*Z*),4-pentadienenitrile (**6**) and its 2(*E*)-isomer as a minor product (R = n-Pr, overall yield 67%, *Z* : *E* = 87 : 13; $R = CH_2CH_2CH_2CH_3$, 50%, 89 : 11; $R = (CH_3)_2CH$, 57%, 67 : 33). The contamination of the *E*-isomers are ascribed to the base-catalyzed isomerization of the primary *Z*-product, whose formation is explained by the following scheme.



Pentadienenitriles (**6**) were also produced from **2** by the treatment with iodine, but overall yield was low.

As the starting materials for the above described procedures are easily available, this novel procedures would be useful for the preparation of 5-monoalkyl-2(*Z*),4(*E*)-pentadienenitriles (**3**), 5,5-dialkyl-2,4-pentadienenitriles (**6**), and 5,5-dialkyl-4-pentenenitriles (**4**). Further transformations of each of these nitriles are open to research in the future.

EXPERIMENTAL

Gas chromatography was performed on Shimadzu GC-4BPT with 3 m × 3 mm glass column packed with 20% polyethyleneglycol and 20% HVSG on Chromosorb W-AW (80–100 mesh). Mass spectra were obtained on Hitachi RMU-6L with 70 eV chamber voltage, NMR were measured on Varian EM-360 and JEOL JNM-PMX 60 with Me_4Si as internal standard and CCl_4 as solvent. IR on Shimadzu IR-27G spectrometer and UV on Hitachi EPS-2.

5-*Alkyl*-5-*dialkylboryl*-2(Z),4(E)-*pentadienenitriles* (**2**). To a soln of 2-bromo-6-lithiopyridine prepared from 2,6-dibromopyridine (0·59 g, 2·5 mmol) in 10 ml of anhyd ether and BuLi (2·75 mmol in 1·85 ml hexane) at −70° through −65° under argon atmosphere,[5] trialkylborane (2·75 mmol) was added at −60°. The mixture was gradually warmed to room temp. Removal of the solvents gave a heavy viscous oil: IR (neat) 2220 cm^{-1}, UV (EtOH) λ_{max} 268 nm (**2**, R = n-Pr).

5-*Alkyl*-2(Z),4(E)-*pentadienenitriles* (**3**). To the above mixture containing **2**, AcOH, (2 ml) was added at room temp. and the resulting mixture was stirred for 2 hr under reflux. The product was extracted with ether and the ethereal extract was washed with water, dried (Na_2SO_4), and column chromatographed (silica gel-benzene). Each nitrile formed a thermally unstable oil. The b.ps of some of them could not be measured.

2(Z),4(E)-*Octadienenitrile* (**3**, R = n-Pr). The overall yield from dibromopyridine was 80%: b.p. 65–75° (5 mm); IR (neat) 2220, 1640, 1580, 990, 950, 740 cm^{-1}; UV (EtOH) λ_{max} 255 nm; MS *m/e* (rel. %) 121 (M^+, 35), 120 (12), 106 (12), 92 (16), 80 (100), 79 (78); NMR (CCl_4) δ ppm, 1·00 (3H, t, J = 7 Hz), 1·50 (2H, sext, J = 7 Hz), 2·30 (2H, apparent q, J = 7·5 Hz), 5·15 (1H, d, J = 11 Hz), 6·0–6·9 (3H, m); $Eu(fod)_3$-shifted NMR [13 mg of 2(*Z*),4(*E*)-octadienenitrile and 55 mg of $Eu(fod)_3$ in 0·35 ml of CCl_4], olefinic protons, δ ppm, 7·08 (1H, d-t, J = 8, 16 Hz), 8·40 (1H, t, J = 11 Hz), 9·60 (1H, d, J = 11 Hz), 10·10 (1H, d-d, J = 11, 16 Hz). (Found: C, 79·14; H, 9·40; N, 11·75. Calc. for $C_8H_{11}N$: C, 79·28; H, 9·15; N, 11·56%).

2(Z),4(E)-*Nonadienenitrile* [**3**, $R = (CH_2)_3CH_3$]. Overall yield from dibromopyridine 93% (calc. by GLC); IR (neat) 2220, 1640, 1580, 990, 950, 740 cm^{-1}; MS *m/e* (rel. %) 135 (M^+, 21), 120 (7), 106 (8), 80 (100), 79 (32); NMR (CCl_4) δ ppm, 0·93 (3H, t, J = 6 Hz), 1·1–1·8 (4H, m), 2·23 (2H, q, J = 6 Hz), 5·08 (1H, d, J = 10 Hz), 6·0–7·0 (3H, m). (Found: C, 80·09; H, 9·84; N, 10·39. Calc. for $C_9H_{13}N$: C, 79·95; H, 9·69; N, 10·36%).

6-*Methyl*-2(Z),4(E)-*heptadienenitrile* [**3**, $R = (CH_3)_2CH$]. Overall yield 60%; IR (neat) 2220, 1640, 1580, 990, 950, 740 cm^{-1}; MS *m/e* (rel. %) 121 (M^+, 37), 120 (18), 106 (50), 80 (28), 79 (100); NMR (CCl_4) δ ppm, 1·08 (6H, d, J = 7 Hz), 2·28 (1H, oct, J = 7 Hz), 5·08 (1H, d, J = 10 Hz), 6·0–7·0 (3H, m). 2-Bromopyridine (yield 8%) was isolated from the mixture.

5,5-*Dialkyl*-4-*pentenenitrile* (**4**). To a soln of 5 - alkyl - 5 - dialkylboryl - 2(*Z*),4(*E*) - pentadienenitrile prepared from 2·5 mmol dibromopyridine, 3 ml of 3 N NaOH was added and the resulting mixture was stirred at room temp. overnight. Ethereal soln was separated, washed with water and dried (Na_2SO_4). Chromatographic separation of the concentrate gave 5,5-dialkyl-4-pentenenitrile.

5-*Propyl*-4-*octenenitrile* (**4**, R = n-Pr). Overall yield 72%. The isolation yield of 94% was realized in an experiment with 10 mmol of the dibromopyridine (4 times scale reaction). IR (neat) 2260, 1662, 1377 cm^{-1}; MS *m/e* (rel. %) 165 (M^+, 13), 150 (6), 137 (22), 122 (25), 109 (33), 95 (31), 83 (57), 81 (42), 69 (100); NMR (CCl_4) δ ppm, 0·92 (6H, t, J = 7 Hz), 1·43 (4H, sext, J = 7 Hz), 2·03 (4H, t, J = 7 Hz), 2·23–2·50 (4H, m), 5·17 (1H, t, J = 6 Hz). (Found: C, 79·37; H, 11·43; N, 8·46. Calc. for $C_{11}H_{19}N$: C, 79·94; H, 11·59; N, 8·48%).

5-*Butyl*-4-*nonenenitrile* [**4**, $R = (CH_2)_3CH_3$]. Overall yield 69%; IR (neat) 2260, 1663, 1378 cm^{-1}; MS *m/e* (rel. %) 193 (M^+, 6), 164 (6), 136 (21), 122 (19), 109 (100), 83 (21), 81 (26), 69 (47); NMR (CCl_4) δ ppm, 0·92 (6H, t, J = 6 Hz), 1·1–1·7 (8H, m), 2·01 (4H, t, J = 7 Hz), 2·20–2·43 (4H, m), 5·10 (1H, t, J = 6 Hz). (Found: C, 80·96; H, 12·20; N, 7·49. Calc. for $C_{13}H_{23}N$: C, 80·76; H, 11·99; N, 7·25%).

5-*Isopropyl*-6-*methyl*-5-*heptenenitrile* [**4**, $R = CH_3)_2CH$]. Overall yield 75% (calcd by GLC); IR (neat) 2260, 1653, 1385, 1368 cm^{-1}; MS *m/e* (rel. %) 165 (M^+, 18), 150 (16), 122 (100), 109 (27), 95 (22), 81 (59), 69 (77); NMR (CCl_4) δ ppm, 1·05 (12H, d, J = 7 Hz), 2·20–2·50 (4H, m), 2·80 (2H, hept, J = 7 Hz), 5·13 (1H, t, J = 6 Hz). (Found: C, 79·99; H, 11·83; N, 8·52. Calc. for $C_{11}H_{19}N$: C, 79·94; H, 11·59; N, 8·48%).

5-*Propyl*-4-*octenal*. To a soln of 1·55 g (9·4 mmol) of 5-propyl-4-octenenitrile in 30 ml toluene, diisobutylaluminium hydride in heptane (14·1 mmol in 18 ml of soln) was added at 0°, followed by heating at 45° overnight. The mixture was treated at 0° with 1·2 ml MeOH, then with 0·54 ml of sat. Na_2SO_4aq. After 45 min stirring, 10 ml of 1 N HCl was added and ppt filtered off. The filtrate was treated furthermore with 20 ml 1 N HCl, followed by stirring at room temp. for 2 hr. The resulting soln was extracted with ether, washed with brine, dried (Na_2SO_4) and concentrated. Column chromatography (Silicagel-benzene) gave 5-propyl-4-octenal (0·98 g, 62% yield).

5,5-*Dialkyl*-2,4-*pentadienenitrile.* To a stirred soln of 5 - alkyl - 5 - dialkylboryl - 2(*Z*),4(*E*) - pentadienenitrile prepared from 2·5 mmol dibromopyridine, 3 ml 3 N NaOH was added and the mixture was treated with 1·27 g (5 mmol in 10 ml ether). After stirring at room temp. overnight, the mixture was extracted with ether, the combined extracts washed with water, dried (Na_2SO_4), and condensed. Pure dienenitrile was obtained by column chromatography (Silicagel).

5-*Propyl*-2,4-*octadienenitrile.* Overall yield from dibromopyridine 67%, the product containing 87% of 2(*Z*)-isomer (**6**, R = n-Pr) and 13% 2(*E*)-isomer. IR (neat) of the mixture, 2225, 1630, 1380, 741 cm^{-1}. (Found: C, 80·67; H, 10·48; N, 8·41. Calc. for $C_{11}H_{17}N$: C, 80·92; H, 10·50; N, 8·58%). The components were isolated by GLC.

2(Z)-*Isomer* (**6**, R = n-Pr). NMR (CCl_4) δ ppm, 0·94 (3H, t, J = 6 Hz), 0·95 (3H, t, J = 6 Hz), 1·13–1·90 (4H, m), 1·90–2·50 (4H, m), 5·03 (1H, d, J = 11 Hz), 6·30 (1H, d, J = 11 Hz), 7·04 (1H, t, J = 11 Hz); MS *m/e* (rel. %) 163 (M^+, 7), 148 (2), 134 (3), 120 (7), 40 (100).

2(E)-*Isomer.* NMR (CCl_4) δ ppm, 0·93 (6H, t, J = 6 Hz), 1·13–1·90 (4H, m), 1·90–2·50 (4H, m), 5·16 (1H, d, J = 16 Hz), 6·10 (1H, d, J = 12 Hz), 7·22 (1H, d-d, J = 12, 16 Hz); MS *m/e* (rel. %) 163 (M^-, 10), 148 (2), 134 (3), 120 (16), 40 (100).

5-*Butyl*-2,4-*nonadienenitrile.* Overall yield from dibromopyridine 50%, the product containing 89% of 2(*Z*)-isomer [**6**, R = $(CH_2)_3CH_3$] and 11% of 2(*E*)-isomer. IR (neat) 2225, 1629, 1382, 740 cm^{-1}. (Found: C, 81·44; H, 11·19; N, 7·55. Calc. for $C_{13}H_{21}N$: C, 81·61; H, 11·06; N, 7·32%).

2(Z)-*Isomer* [**6**, R = $(CH_2)_3CH_3$]. NMR (CCl_4) δ ppm, 0·93 (6H, t, J = 6 Hz), 1·10–1·80 (8H, m), 1·80–2·50 (4H, m), 5·05 (1H, d, J = 11 Hz), 6·27 (1H, d, J = 12 Hz), 7·03 (1H, t, J = 11 Hz); MS *m/e* (rel. %) 191 (M^+, 38), 162 (10), 148 (12), 134 (26), 120 (26), 107 (43), 93 (38), 80 (100), 79 (57), 67 (57).

2(E)-*Isomer.* MS *m/e* (rel. %) 191 (M^+, 38), 162 (10), 148 (10), 134 (25), 120 (25), 107 (40), 93 (35), 80 (100), 79 (52), 67 (51).

5-*Isopropyl*-6-*methyl*-2,4-*heptadienenitrile.* Overall yield 57%, the product containing 67% of 2(*Z*)-isomer [**6**, R = $(CH_3)_2CH$] and 33% of 2(*E*)-isomer. IR (neat) 2230, 1625, 1385, 1365, 740 cm^{-1}. (Found: C, 80·93; H, 10·49; N, 8·64. Calc. for $C_{11}H_{17}N$: C, 80·92; H, 10·50; N, 8·58%).

2(Z)-*Isomer* [**6**, R = $(CH_3)_2CH$]. NMR δ ppm, 1·10 (6H, d, J = 7 Hz), 1·11 (6H, d, J = 7 Hz), 2·53 (1H, hept, J = 7 Hz), 3·09 (1H, hept, J = 7 Hz), 5·08 (1H, d, J = 11 Hz), 6·32 (1H, d, J = 12 Hz), 7·22 (1H, t, J = 12 Hz); MS *m/e* (rel. %) 163 (M^+, 22), 148 (4), 121 (93), 120 (88), 106 (92), 93 (69), 79 (49), 70 (100), 43 (81).

2(E)-*Isomer.* NMR (CCl_4) δ ppm, 1·10 (6H, d, J = 7 Hz), 1·11 (6H, d, J = 7 Hz), 2·53 (1H, hept, J = 7 Hz), 3·09 (1H, hept, J = 7 Hz), 5·20 (1H, d, J = 16 Hz), 5·92 (1H, d, J = 12 Hz), 7·38 (1H, d-d, j = 12, 16 Hz); MS *m/e* (rel. %) 163 (M^-, 23), 148 (4), 121 (76), 120 (95), 106 (76), 93 (65), 79 (44), 70 (100), 43 (89).

Treatment of 5 - dipropylboryl - 2(Z),4(E) - *octadienenitrile* (**2**, R = n-Pr) *with iodine.* To a soln of 5 - dipropylboryl - 2(*Z*),4(*E*) - octadienenitrile prepared from 2·5 mmol 2,6-dibromopyridine, a soln of 1·27 g (5 mmol) I_2 in 10 ml ether was added and the resulting mixture was stirred overnight at room temp. To the resulting soln was added 3 ml of 3 N NaOH and the mixture was stirred for 1 hr at room temp. A mixture of 5-propyl-2,4-octadienenitrile was obtained in 26% overall yield (containing 20% of 2(*Z*)-isomer and 80% of 2(*E*)-isomer).

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