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The *N*-vinyl group as a protection group of the preparation of 3(5)-substituted pyrazoles via bromine–lithium exchange

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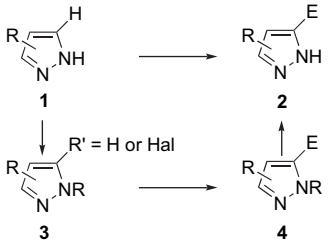
Abstract—Treatment of 3,4,5-tribromopyrazole with 1,2-dibromoethane and triethylamine gave 3,4,5-tribromo-1-vinylpyrazole, which underwent regioselective bromine–lithium exchange at the 5-position. Subsequent addition of an electrophile gave 5-substituted 3,4-dibromo-1-vinylpyrazoles. These underwent bromine–lithium or bromine–magnesium exchange predominantly at the 4-position, with the regioselectivity between the 3- and 4-positions being influenced by the nature of the metal and the 5-substituent. The 5-substituted products were de-vinylated by mild treatment with $KMnO_4$ affording 3-substituted pyrazoles. Alternatively, the 1-vinyl group could be used in ring-closing metathesis. Thus, 5-allylthio-1-vinylpyrazole produced 5*H*-pyrazolo[5,1-*b*][1,3]thiazine upon treatment with Grubbs' second-generation catalyst.

1. Introduction

Only few methods for the direct introduction of substituents into the 3-position of pyrazoles to give 3-substituted pyrazoles (**2**) have been reported, and in these cases the observed yields are usually low.[1,2] For example, proton–lithium exchange of pyrazole (**1**, R=H) using butyl or phenyllithium followed by the addition of carbon dioxide produced only 9% of 3-carboxypyrazole (**2**, R=H, E=COOH).[3] Bromine–lithium exchange of 3,4,5-tribromopyrazole (**5**) took place in the undesired 4-position, and subsequent trapping with carbon dioxide produced the corresponding 3,5-dibromo-4-carboxypyrazole (Scheme 1).[3]



Scheme 1.

Another approach to **2** utilises the *N*-protected pyrazoles (**3**) that undergo regioselective proton–metal or halogen–metal exchange at the 5-position. The subsequent trapping with electrophiles gives the 1,5-disubstituted pyrazoles (**4**),[3,4] which after final removal of the *N*-protecting group leads to the desired 3-substituted pyrazoles (**2**).

Previously, the pyrazole nitrogen has been protected during lithiation with a range of protecting groups including SEM,[5–8] THP,[9,10] Bn,[3,11] SO_2NMe_2,[12–14] SO_2Ph,[15–17] Tos,[18] Trt,[19] 1,1-diethoxyethyl,[20] PMB[6] and OBn.[21,22] All of these groups require treatment with acid,[23–25] base[17,26] or sodium metal,[3,24] except for the OBn group, which can be removed by mild hydrogenolysis.[21]

In our search for a complementary protecting group, which can be removed by oxidation under mild and neutral conditions, we have investigated the vinyl group, which has been used previously in the imidazole series.[27]

2. Results and discussion

N-Vinyl-3,4,5-tribromopyrazole **6** was chosen as the starting material since it allows for bromine–metal exchange in all positions, in contrast to *N*-protected pyrazole (**3**, R=R′=H), which only undergoes proton–metal exchange at the 5-position.[4] For consecutive introduction of additional substituents in **6**, the regioselectivity in the second halogen–metal

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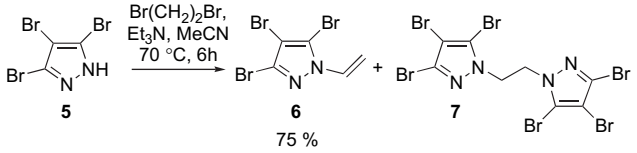
exchange reaction must be known. Therefore, a series of 5-substituted *N*-vinyl-3,4-dibromopyrazoles was subjected to halogen–metal exchange.

First, pyrazole was brominated to give 3,4,5-tribromopyrazole **5** in 68% yield. For the vinylation we then chose a method employing cheap and readily available starting materials suitable for large-scale synthesis, even though a promising copper-mediated vinylation method has been reported recently.[28] Hence, alkylation of **5** with 1,2-dibromoethane in the presence of triethylamine followed by the elimination of HBr gave 3,4,5-tribromo-1-vinylpyrazole **6** in 75% overall yield. Substitution of both bromine atoms of 1,2-dibromoethane with the formation of 1,2-bis(3,4,5-tribromopyrazol-1-yl)ethane **7** was best suppressed by performing the reaction in acetonitrile using a large excess of triethylamine (Scheme 2).

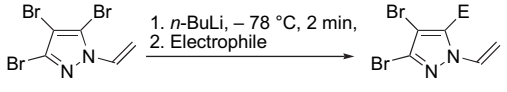


Scheme 2.

Studies of the bromine–lithium exchange of **6** showed that it was best effected using 1.1 equiv of *n*-BuLi at −78 °C. The electrophile was then added after ca. 2 min to give the 5-substituted 3,4-dibromo-1-vinylpyrazoles **8–18** in good yields (Table 1). In this way, a range of electrophiles could be introduced at the 5-position. Longer lithiation time (10–15 min) led to lower yields of the 5-substituted products, reflecting the limited stability of the pyrazole anion. When tosyl cyanide was used as the electrophile, the yield of cyanation dropped to 26%. Presumably, the pyrazole anion acts as a base abstracting one of the methyl protons in the tosyl group.

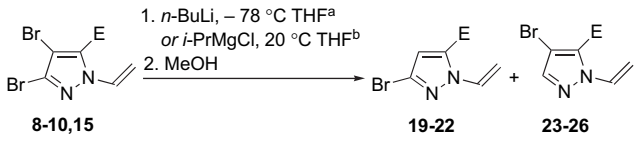
The regioselectivity of bromine–lithium and bromine–magnesium exchange in the 5-substituted 3,4-dibromo-1-vinylpyrazoles **8–10** and **15** was studied using *n*-BuLi or *i*-PrMgCl for the bromine–metal exchange together with protons from methanol as the electrophile.

Table 1. Bromine–lithium exchange of **6** followed by the addition of electrophile



Electrophile	Product	E	Yield (%)
NH_4Cl	**8**	H	80
Cl_6C_2	**9**	Cl	82
MeI	**10**	Me	78
DMF	**11**	CHO	66
Ph_2CO	**12**	$CHPh_2OH$	81
TsCN	**13**	CN	26
TBDMSCl	**14**	TBDMS	77
Me_2S_2	**15**	SMe	84
All_2S_2	**16**	SAll	77
Ph_2PCl	**17**	PPh_2	59
Bu_3SnCl	**18**	$SnBu_3$	77

Table 2. Bromine-lithium exchange and bromine–magnesium exchange of 5-substituted 3,4-dibromo-1-vinylpyrazoles **8–10** and **15**



Starting material	E	Conditions	Product(s)	Ratio[c]	Yield[d]
8	H	[a]	**19+23**	93:7	[e]
8	H	[b]	**19+23**	81:19	[e]
9	Cl	[a]	**20+24**	>99:1	36
9	Cl	[b]	**20+24**	>99:1	12
11	Me	[a]	**21+25**	97:3	16
11	Me	[b]	**21+25**	82:18	13
15	SMe	[a]	**22+26**	98:2	35
15	SMe	[b]	**22+26**	>99:1	40

[c] Determined by GC–MS and ^{1}H NMR of the crude reaction mixture.
[d] Non-optimized isolated yield of major constituent.
[e] Not determined.

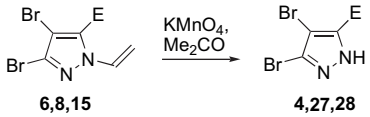
Bromine–metal exchange of 5-substituted 3,4-dibromopyrazoles **8–10** and **15** took place predominantly at C-4 to give **19–22**, all displaying a characteristic NMR signal from H-4 in the 6.1–6.3 ppm range[29] (Table 2).

It turns out that bromine–lithium exchange takes place with higher regioselectivity than bromine–magnesium exchange (Table 2). In addition, it is observed that the 5-substituent influences the regioselectivity. In agreement with previous reports, both the chlorine[30] and methylthio[31,32] groups have an ortho-directing effect giving rise to an increase in 4-substitution. However, the methyl group which usually is considered not to be ortho-directing,[30] gives rise to increased bromine–lithium exchange in the 4-position, despite it having no chelating properties and would be expected rather to promote 3-substitution due to its bulkiness.

Further bromine–metal exchange of the 3-bromopyrazoles **19–22** was not investigated since this has been described for *N*-methyl 3-bromopyrazoles.[33]

The vinyl group of 3,4,5-tribromo-1-vinylpyrazole **6** and 3,4-dibromo-1-vinylpyrazole **8** could be removed smoothly in excellent yield by treatment with a 2% solution of potassium permanganate (Table 3). The reaction was

Table 3. Oxidative removal of the 1-vinyl group of pyrazoles

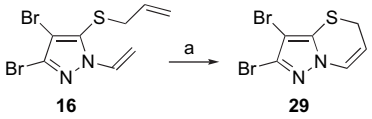


Starting material	E	Temp (°C)	Product	Yield (%)
6	Br	20	**4**	96
8	Me	20	**27**	96
15	SMe	20	**28**	49[a]
15	SMe	0	**28**	64[b]
15	SMe	−20 to −10	**28**	86[c]

[a] Only the product resulting from simultaneous oxidation of SMe to SO_2Me was observed.
[b] SMe–SO_2Me (1:1).
[c] Only SMe was observed.

instantaneous both at room temperature and at −10 °C making it possible to perform the deprotection as a titration. The oxidation sensitive SMe-substituted compound **15** had to be de-vinylated at −20 to −10 °C producing **28** in 86% yield. At higher temperatures, concurrent oxidation of SMe to SO_2Me was observed.

Like previously reported,[28] the pyrazole *N*-vinyl group could be used in ring-closing metathesis. Thus, microwave irradiation of **16** with Grubbs' second-generation catalyst,[34] which in this reaction was more reactive than Grubbs' first generation[35,36] and the Hoveyda–Grubbs' catalyst,[37] gave 5*H*-pyrazolo[5,1-*b*][1,3]thiazine **29** in 83% yield (Scheme 3).



16 29

Scheme 3. Reagents and conditions: (a) (1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene)(tricyclohexylphosphine)-ruthenium, MW, 140 °C, 10 min.

3. Conclusion

It has been demonstrated that the vinyl group is a stable and versatile N-protection group in pyrazoles, and that it can be removed easily by oxidation with $KMnO_4$ under mild conditions. Metal–halogen exchange in 1-substituted 3,4,5-tribromopyrazole **6** was regioselective for the 5-position enabling the incorporation of a wide range of electrophiles at C-5. Halogen–metal exchange of 5-substituted 3,4-dibromopyrazoles **9**–**10** and **15** took place predominantly at the 4-position with the ortho-directing effect of the 5-substituent decreasing in the order Cl>SMe>Me. In addition, it was observed that bromine–lithium exchange took place with higher regioselectivity than bromine–magnesium exchange.

These results enable the consecutive introduction of substituents in *N*-protected 3,4,5-tribromopyrazoles like **6** to give 3-substituted pyrazoles (**2**) as the final products. The 1-vinyl group of 5-allylthio-1-vinylpyrazole **16** underwent ring-closing metathesis under microwave heating in the presence of Grubbs' second-generation catalyst producing 5*H*-pyrazolo[5,1-*b*][1,3]thiazine **29**.

4. Experimental

4.1. General methods

All reactions involving air-sensitive reagents were performed under nitrogen using syringe-septum cap techniques. All glassware was flame-dried prior to use. Solutions were dried with magnesium sulfate. Solvents were removed in vacuo below 40 °C by rotary evaporation. Flash chromatography[38] was performed using silica gel Merck 60 (70–230 mesh). Melting points are uncorrected. All new compounds were colourless, unless otherwise stated. ^1H and ^{13}C NMR spectra were recorded on a 300 MHz instrument in $CDCl_3$ at 300 and 75 MHz with Me_4Si (^1H) or the solvent signal (^{13}C) as internal standard. R_f values are given for ethyl acetate–heptanes (1:10), unless otherwise stated. Microwave-assisted synthesis was carried out in an initiator single-mode microwave cavity producing controlled irradiation at 2.45 GHz (Biotage AB, Uppsala).

4.2. Materials

All solvents and reagents were obtained from Fluka or Aldrich and used without further purification with the following exceptions: THF was distilled from Na/benzophenone ketyl under nitrogen. *n*-Butyllithium was titrated prior to use.[39] DMF was distilled from phosphorus pentoxide and stored over 3 Å molecular sieves.[40] Dimethyl disulfide and diallyl disulfide were filtered through neutral alumina and kept under argon with 3Å molecular sieves.[41] Hexachloroethane was recrystallized from ethanol, dissolved in toluene and concentrated in vacuo until complete dryness.[41] A 75 w/w% solution in THF was prepared and kept under argon with 3 Å molecular sieves.

4.2.1. 3,4,5-Tribromopyrazole 5. Bromine (45.5 mL, 891 mmol) in glacial acetic acid (50 mL) was added dropwise to a stirred mixture of pyrazole (20.02 g, 294 mmol) and anhydrous sodium acetate (96.4 g, 1.19 mol) in glacial acetic acid (550 mL). Stirring was continued for 60 h at ambient temperature. After removal of the solvent, water (500 mL) was added and the suspension stirred thoroughly for 2 h. The water was removed by filtration, and the procedure was repeated with another 500 mL of water. The solid was recrystallized in ethanol–water and dried overnight at room temperature. This gave 61.2 g (68%) of 3,4,5-tribromopyrazole **5**, mp 182–183 °C (lit.[42,43] mp 184, 188 °C).

4.2.2. 3,4,5-Tribromo-1-vinylpyrazole 6. 3,4,5-Tribromopyrazole **5** (10.0 g, 32.8 mmol), 1,2-dibromoethane (28.2 mL, 328 mmol), triethylamine (366 mL, 2.62 mol) and acetonitrile (366 mL) were stirred at 70 °C for 6 h. Removal of the solvent, addition of dichloromethane (100 mL), washing with water (3×100 mL), drying and removal of the dichloromethane gave 8.50 g of compound **6** containing a small amount of 1,2-bis(3,4,5-tribromopyrazol-1-yl)ethane **7**. Recrystallization twice from heptanes afforded 6.78 g (62%) of 3,4,5-tribromo-1-vinylpyrazole **6** (R_f=0.64) as slightly yellow crystals, mp 79–80 °C. Alternative purification of the crude product by flash chromatography (ethyl acetate–heptanes, 1:10) gave 7.9 g (75%) of 3,4,5-tribromo-1-vinylpyrazole **6**, mp 79–80 °C. δ_H ($CDCl_3$): 7.05 (1H, dd, J=15 and 9 Hz, CH), 5.86 (1H, d, J=15 Hz, CH_2), 5.02 (1H, d, J=9 Hz, CH_2). δ_C ($CDCl_3$): 130.9 (C-3), 129.0 (CH), 116.0 (C-5), 104.3 (CH_2), 101.3 (C-4). Anal. Calcd for $C_5H_3N_2Br_3$: C, 18.15; H, 0.91; N, 8.47. Found: C, 18.27; H, 0.94; N, 8.54%.

4.2.3. 1,2-Bis(3,4,5-tribromopyrazol-1-yl)ethane 7. 3,4,5-Tribromopyrazole **5** (500 mg, 1.6 mmol), triethylamine (245 μL, 1.76 mmol) and acetonitrile (5 mL) were stirred at 70 °C for 4 h, then 1,2-dibromoethane (85 μL, 0.98 mmol) was added. Stirring at 70 °C for 2.5 h and at room temperature for 16 h, removal of the solvent, addition of dichloromethane (20 mL), washing with water (4×20 mL), drying and evaporation of the dichloromethane gave 517 mg of crystals, which contained 1,2-bis(3,4,5-tribromopyrazol-1-yl)ethane **7**, 1-(2-bromoethyl)-3,4,5-tribromopyrazole and 3,4,5-tribromo-1-vinylpyrazole **6** in the ratio 44:36:20 (^1H NMR). Addition of acetone (20 mL), filtration and recrystallization from heptanes gave pure **7**. Mp>240 °C. δ_H ($CDCl_3$): 4.57

(1H, s). Anal. Calcd for $C_8H_4N_4Br_6$: C, 15.12; H, 0.63; N, 8.82. Found: C, 15.28; H, 0.48; N, 8.65%.

4.3. Lithiation followed by reaction with an electrophile. General procedure

n-Butyllitium (1.68 M in hexanes, 460 μL, 0.77 mmol) was added dropwise at −78 °C over a period of 2 min to a stirred solution of 3,4,5-tribromo-1-vinylpyrazole **6** (232 mg, 0.70 mmol) in dry THF (5 mL). Stirring was continued for 1 min, whereupon the electrophile was added. After stirring at −78 °C for 1 h, the temperature was allowed to reach room temperature during ca. 1 h. After a further 0.5 h at room temperature, saturated aq NH_4Cl (2 mL) was added. Stirring for another 5 min, addition of water (8 mL) and dichloromethane (10 mL), isolation of the organic layer, further extraction of the aqueous phase with dichloromethane (3×10 mL), drying of the combined organic solutions and removal of the dichloromethane gave a crude product, which was purified by flash chromatography using ethyl acetate–heptanes (1:10) as the eluent, unless otherwise stated.

4.3.1. 3,4-Dibromo-1-vinylpyrazole 8. Lithiation of 3,4,5-tribromo-1-vinylpyrazole **6** (232 mg) according to the general procedure was followed by quenching with saturated NH_4Cl (2 mL). The mixture was immediately allowed to warm to room temperature. Work-up and flash chromatography provided 141 mg (80%) of **8** (R_f=0.31), mp 37–38 °C (heptanes). δ_H ($CDCl_3$): 7.58 (1H, s, H-5), 6.89 (1H, dd, J=15 and 9 Hz, CH), 5.53 (1H, dd, J=15 and 1.5 Hz, CH_2), 4.90 (1H, dd, J=9 and 1.5 Hz, CH_2). δ_C ($CDCl_3$): 131.9 (C-5), 130.0 (C-3), 128.8 (CH), 101.2 (CH_2), 98.4 (C-4). Anal. Calcd for $C_5H_4N_2Br_2$: C, 23.84; H, 1.60; N, 11.12. Found: C, 23.87; H, 1.62; N, 11.07%.

4.3.2. 3,4-Dibromo-5-chloro-1-vinylpyrazole 9. Using the general method with hexachloroethane (75 w/w% solution in THF, 1.1 mL, 3.5 mmol) as the electrophile, work-up and flash chromatography (dichloromethane–heptanes, 1:5) gave 165 mg (82%) of **9** as a light sensitive white solid. δ_H ($CDCl_3$): 7.05 (1H, dd, J=15 and 9 Hz, CH), 5.86 (1H, d, J=15 Hz, CH_2), 5.02 (1H, d, J=9 Hz, CH_2). δ_C ($CDCl_3$): 130.3, 127.8, 127.6, 104.0, 97.5. HRMS (EI+) calcd for $[M]^+$ 283.8352. Found, 283.8322.

4.3.3. 3,4-Dibromo-5-methyl-1-vinylpyrazole 10. The general method with methyl iodide (220 μL, 3.5 mmol) as the electrophile was used. Work-up and flash chromatography provided 117 mg (78%) of **10** as a slightly volatile oil. δ_H ($CDCl_3$): 6.90 (1H, dd, J=15 and 9 Hz, CH), 5.76 (1H, d, J=15 Hz, CH_2), 4.92 (1H, d, J=9 Hz, CH_2), 2.40 (3H, s, Me). δ_C ($CDCl_3$): 138.0 (C-5), 129.5 (C-3), 128.7 (CH), 102.6 (CH_2), 97.9 (C-4), 10.5 (CH_3). HRMS (FAB+) calcd for $[M+H]^+$ 264.8976. Found, 264.8984.

4.3.4. 3,4-Dibromo-5-formyl-1-vinylpyrazole 11. The general procedure with *N*,*N*-dimethylformamide (0.27 mL, 3.5 mmol) as the electrophile was used. The mixture was worked up by stirring at room temperature for 1 h with 1 M HCl (2 mL). Addition of water (8 mL) and K_2CO_3 until alkaline followed by extraction with dichloromethane (3×10 mL), drying, removal of the dichloromethane and flash chromatography provided 130 mg (66%) of slightly hygroscopic **11**, (R_f=0.53), mp 67–68 °C (heptanes). δ_H ($CDCl_3$): 9.84 (1H, s, CHO), 7.85 (1H, dd, J=15 and 9 Hz, CH), 5.95 (1H, d, J=15 Hz, CH_2), 5.09 (1H, d, J=9 Hz, CH_2). Anal. Calcd for $C_6H_4ON_2Br_2$: C, 25.74; H, 1.44; N, 10.01. Found: C, 25.87; H, 1.48; N, 10.01%.

4.3.5. 3,4-Dibromo-5-(hydroxydiphenylmethyl)-1-vinylpyrazole 12. Using the general method with benzophenone (153 mg, 0.84 mmol) in dry THF (3 mL) as the electrophile, work-up and flash chromatography provided 247 mg (81%) of **12** (R_f=0.3), mp 126–127 °C (heptanes). δ_H ($CDCl_3$): 7.38–7.12 (11H, m, Ph and CH), 5.62 (1H, d, J=15 Hz, CH_2), 4.62 (1H, d, J=9 Hz, CH_2), 3.34 (1H, s, OH). Anal. Calcd for $C_{18}H_{14}N_2OBr_2$: C, 49.80; H, 3.25; N, 6.45. Found: C, 50.00; H, 3.30; N, 6.33%.

4.3.6. 3,4-Dibromo-5-cyano-1-vinylpyrazole 13. Using the general method with 3,4,5-tribromo-1-vinylpyrazole (100 mg, 0.30 mmol) and tosyl cyanide (125 mg, 0.69 mmol) in THF (5 mL) as the electrophile, work-up and flash chromatography provided 22 mg (26%) of **13** (R_f=0.62), mp 83–84 °C. δ_H ($CDCl_3$): 7.08 (1H, dd, J=15 and 8 Hz, vinyl-CH), 5.97 (1H, dd, J=15 and 2 Hz, vinyl-CH_2), 5.2 (1H, dd, J=9 and 2 Hz, vinyl-CH_2). δ_C ($CDCl_3$): 131.1, 129.7, 116.8, 108.3, 107.4, 106.5. Anal. Calcd for $C_6H_3N_3Br_2$: C, 26.02; H, 1.09; N, 15.17. Found: C, 26.37; H, 0.78; N, 14.90%.

4.3.7. 3,4-Dibromo-5-*tert*-butyldimethylsilyl-1-vinylpyrazole 14. Using the general method with *tert*-butyldimethylchlorosilane (211 mg, 1.4 mmol) dissolved in THF (2 mL) as the electrophile, the chromatographic separation gave 197 mg (77%) of **14** (R_f=0.65) as an oil, which was reprecipitated from heptanes. δ_H ($CDCl_3$): 7.0 (1H, dd, J=15 and 8 Hz, CH), 5.79 (1H, d, J=15 Hz, CH_2), 4.88 (1H, d, J=8 Hz, CH_2), 0.93 (9H, s, CMe_3), 0.48 (6H, s, $SiMe_2$). Anal. Calcd for $C_{11}H_{18}N_2Br_2Si$: C, 36.08; H, 4.95; N, 7.65. Found: C, 35.99; H, 4.95; N, 7.63%.

4.3.8. 3,4-Dibromo-5-methylthio-1-vinylpyrazole 15. Using the general method with dimethyl disulfide (189 μL, 2.10 mmol) as the electrophile, flash chromatography gave 175 mg (84%) of **15** (R_f=0.54) as an oil, which was recrystallized from heptanes with cooling to −78 °C, mp<20 °C. δ_H ($CDCl_3$): 7.42 (1H, dd, J=15 and 9 Hz, CH), 5.85 (1H, d, J=15 Hz, CH_2), 4.98 (1H, d, J=9 Hz, CH_2), 2.39 (3H, s, SMe). δ_C ($CDCl_3$): 136.5, 130.7, 129.1, 106.3, 103.4, 18.8. Anal. Calcd for $C_6H_6N_2SBr_2$: C, 24.18; H, 2.03; N, 9.40. Found: C, 24.14; H, 2.08; N, 9.30%.

4.3.9. 5-Allylthio-3,4-dibromo-1-vinylpyrazole 16. Using the general method with diallyl disulfide (500 μL, 3.45 mmol) as the electrophile, flash chromatography gave 175 mg (77%) of **16** (R_f=0.42) as an oil. δ_H ($CDCl_3$): 7.36 (1H, dd, J=15 and 9 Hz), 5.85–5.67 (2H, m), 5.02–4.87 (3H, m), 3.39 (2H, d, J=8 Hz, SCH_2). δ_C ($CDCl_3$): 134.4, 132.2, 130.5, 129.2, 119.6, 107.3, 103.1, 54.6, 38.9. Anal. Calcd for $C_8H_8N_2SBr_2$: C, 29.65; H, 2.49; N, 8.65. Found: C, 29.38; H, 2.65; N, 8.38%.

4.3.10. 3,4-Dibromo-5-diphenylphosphanyl-1-vinylpyrazole 17. Using the general method with 3,4,5-tribromo-1-vinylpyrazole (198 mg, 0.60 mmol) and chlorodiphenylphosphane (0.55 mL, 3.06 mmol) as the electrophile,

work-up and flash chromatography gave 155 mg (59%) of **17** (R_f=0.60) as an oil. δ_H ($CDCl_3$): 7.72–6.96 (11H, m), 5.74 (1H, dd, J=15 and 2 Hz), 4.79 (1H, d, J=9 Hz). δ_C (C_6D_6): 137.6 (d, J_{CP}=30 Hz), 133.0 (d, J_{CP}=20 Hz), 131.9 (d, J_{CP}=6 Hz), 130.5 (d, J_{CP}=10 Hz), 129.2 (d, J_{CP}=22 Hz), 108.2, 103.1. HRMS (EI+) calcd for $[M]^+$ 433.9183. Found, 433.9171.

4.3.11. 3,4-Dibromo-5-tributylstannyl-1-vinylpyrazole 18. Using the general method for lithiation with tributylchlorostannane (228 μL, 0.84 mmol) as the electrophile, the chromatographic separation gave 293 mg (77%) of **18** as an oil, which was further purified by ball-tube distillation at 181 °C and 0.02 mmHg. The compound was unstable and a correct elemental analysis could not be obtained. δ_H ($CDCl_3$): 6.77 (1H, dd, J=15 and 9 Hz, CH), 5.76 (1H, d, J=15 Hz, CH_2), 4.84 (1H, d, J=9 Hz, CH_2), 1.58–1.45 (6H, m, $SnCH_2$), 1.37–1.21 (12H, m, CH_2CH_2), 0.88 (9H, t, J=7 Hz, Me).

4.3.12. 2,3-Dibromo-5*H*-pyrazolo[5,1-*b*][1,3]thiazine 29. To a solution of 5-allylthio-3,4-dibromo-1-vinylpyrazole **16** (100 mg, 0.31 mmol) in toluene (5 mL) was added (1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro-(phenylmethylene)(tricyclohexylphosphine)ruthenium (26 mg, 0.03 mmol) and the mixture was heated to 140 °C under microwave irradiation for 10 min. To the mixture was added $Pb(OAc)_4$ (20 mg, 0.04 mmol), and the reaction was stirred overnight. Then the mixture was filtered through a pad of silica, and filtration provided 76 mg (83%) of **29** (R_f=0.35), mp 88–89 °C. δ_H ($CDCl_3$): 6.94 (1H, dt, J=1.6 and 8.2 Hz), 5.41 (1H, dt, J=5.2 and 8.2 Hz), 3.55 (2H, dd, J=1.6 and 5.2 Hz). δ_C ($CDCl_3$): 133.4, 130.1, 128.0, 106.1, 96.0, 23.4. Anal. Calcd for $C_6H_4N_2SBr_2$: C, 24.35; H, 1.36; N, 9.46. Found: C, 24.28; H, 1.50; N, 9.28%.

4.4. Lithiation of 5-substituted 3,4-dibromo-1-vinylpyrazoles. General procedure

3,4-Dibromo-5-methyl-1-vinylpyrazole **10** (69 mg, 0.26 mmol) was lithiated according to the general procedure. After 1 min, methanol (1 mL) was added. According to GC–MS, the distribution between 3-bromo-5-methyl-1-vinylpyrazole **21** and 4-bromo-5-methyl-1-vinylpyrazole **25** was 97:3, while only **21** could be observed by ^1H NMR. The mixture was evaporated to dryness and subjected to flash chromatography (dichloromethane–pentanes 1:1) providing 8 mg (16%) of the major isomer **21** as a volatile oil. δ_H ($CDCl_3$): 6.85 (1H, dd, J=15.2 and 8.6 Hz), 6.10 (1H, s), 5.72 (1H, d, J=15.2 Hz), 4.88 (1H, d, J=8.6 Hz), 2.32 (3H, s). δ_C ($CDCl_3$): 140.5, 128.5, 109.4, 101.9, 10.9. HRMS (EI+) calcd for $[M]^+$ 185.9793. Found, 185.9794.

Similarly, 3,4-dibromo-1-vinylpyrazole **8** (20 mg, 0.08 mmol) afforded **19**. δ_H ($CDCl_3$): 7.44 (1H, d, J=2.6 Hz), 6.88 (1H, dd, J=8.8, 15.5 Hz), 6.29 (1H, d, J=2.3 Hz), 5.49 (1H, dd, J=14.0, 1.7 Hz), 4.79 (1H, dd, J=9.1, 1.5 Hz). HRMS (ES+) calcd for $[M+H]^+$ 172.9714. Found, 172.9709.

Similarly, 3,4-dibromo-5-chloro-1-vinylpyrazole **9** (69 mg, 0.24 mmol) after flash chromatography (dichloromethane–pentanes 1:1) provided 18 mg (36%) of **20** as a volatile oil. δ_H ($CDCl_3$): 6.98 (1H, dd, J=8.8 and 15.3 Hz), 6.24 (1H, s), 5.75 (1H, d, J=15.2 Hz), 4.93 (1H, d, J=8.8 Hz). δ_C ($CDCl_3$): 127.5, 127.0, 126.2, 107.4, 102.5. HRMS (EI+) calcd 205.9246. Found, 205.9244.

Similarly, 3,4-dibromo-5-methylthio-1-vinylpyrazole **15** (66 mg, 0.22 mmol) after flash chromatography (dichloromethane–pentanes 1:1) provided 17 mg (35%) of **22** as a volatile oil. δ_H ($CDCl_3$): 7.19 (1H, dd, J=8.8 and 15.3 Hz), 6.34 (1H, s), 5.79 (1H, d, J=15.3 Hz), 4.93 (1H, d, J=8.82 Hz), 2.36 (3H, s). δ_C ($CDCl_3$): 139.2, 128.8, 128.7, 112.2, 102.6, 19.9. HRMS (EI+) calcd for $[M]^+$ 217.9513. Found, 217.9522.

4.5. Magnesiation of 5-substituted 3,4-dibromo-1-vinylpyrazoles. General procedure

To a solution of 3,4-dibromo-5-methylthio-1-vinylpyrazole **15** (85 mg, 0.29 mmol) in THF (5 mL) at 20 °C was added dropwise *i*-PrMgCl (2.0 M in THF, 0.15 mL, 0.30 mmol). After stirring for 5 min, methanol (1 mL) was added. According to GC–MS, the ratio between 3-bromo-5-methylthio-1-vinylpyrazole **21** and 4-bromo-5-methylthio-1-vinylpyrazole **21** was higher than 99:1, while only **21** could be observed by ^1H NMR. Flash chromatography (dichloromethane–pentanes 1:1) provided 7 mg (12%) of the major isomer **21** as a volatile oil.

Compounds **8**–**10** were magnesiated in the same fashion.

4.6. De-vinylation of 5-substituted 3,4-dibromo-5-methyl-1-vinylpyrazoles. General procedure

With stirring at 20 °C, a freshly prepared 2% aqueous solution of $KMnO_4$ (3.5 mL, 0.44 mmol) was added at once to a solution of 3,4,5-tribromo-1-vinylpyrazole **6** (50 mg, 0.15 mmol) in acetone (5 mL). Decolouration was complete in 2 min at which time TLC indicated that all starting materials had reacted. Filtration, extraction with acetone (2×5 mL) and evaporation to dryness gave a residue, which was dissolved in ethyl acetate (20 mL) and water (20 mL). The organic solution was isolated and washed with water (10 mL). The combined water solutions were back-extracted with ethyl acetate (10 mL). The combined organic solutions were then dried, and the solvents removed to afford 44 mg (96%) of 3,4,5-tribromopyrazole **5**, mp 182.0–182.1 °C.

Similarly, 3,4-dibromo-5-methyl-1-vinylpyrazole **8** (91 mg, 0.34 mmol) afforded 79 mg (96%) of 3,4-dibromo-5-methylpyrazole **27**, mp 138–140 °C. δ_H ($CDCl_3$): 2.40 (s, CH_3). δ_C ($CDCl_3$): 140.6, 128.0, 96.4, 10.5. Anal. Calcd for $C_4H_4N_2Br_2$: C, 20.03; H, 1.68; N, 11.68. Found: C, 20.08; H, 1.36; N, 11.48%.

A freshly prepared 0.04% solution of $KMnO_4$ in acetone (32 mL, 0.81 mmol) was added dropwise to a −20 °C solution of 3,4-dibromo-5-methylthio-1-vinylpyrazole **15** (79 mg, 0.27 mmol) in acetone (10 mL). The solution was allowed to reach −10 °C over 1 h and stirred for a further 4 h. To the reaction mixture was added water (30 mL) and the aqueous layer was extracted with ethyl acetate (3×30 mL). The combined organic phases were dried and evaporated to yield 64 mg (86%) of 3,4-dibromo-5-methylthio-1-vinylpyrazole **28** as a white solid, mp 109–110 °C.

δ_H ($CDCl_3$): 2.43 (s, CH_3). δ_C ($CDCl_3$): 138.5, 128.5, 113.0, 18.0. Anal. Calcd for $C_4H_4Br_2N_2S$: C, 17.67; H, 1.48; N, 10.30. Found: C, 17.92; H, 1.63; N, 10.22%.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.10.009.

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