Pergamon

Tetrahedron 57 (2001) 2133–2138

TETRAHEDRON

# The tellurium–lithium exchange reaction: selective functionalization of electron-deficient heteroaromatics

Osamu Sugimoto, Muneyoshi Sudo and Ken-ichi Tanji*

*Laboratory of Organic Chemistry, School of Food and Nutritional Sciences, University of Shizuoka, 52-1 Yada, Shizuoka 422-8526, Japan*

Received 18 December 2000; accepted 15 January 2001

**Abstract**—Electron-deficient heteroaromatic tellurides, which was obtained from the corresponding haloheteroaromatics, reacted selectively with *n*-butyllithium to give the lithio derivatives. 

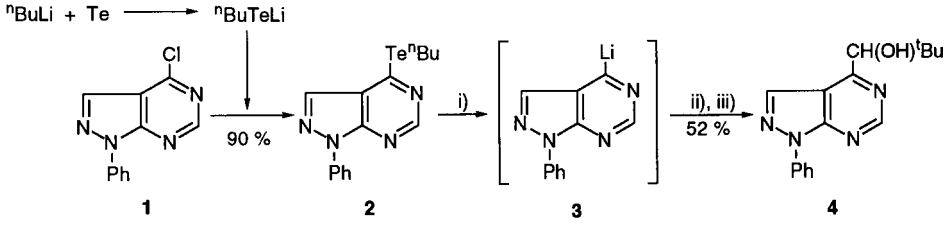
## 1. Introduction

A number of studies on the lithiation of heteroaromatics have been reported in review form,[1,2] however, data on the lithiation of electron-deficient heteroaromatics is sparse, and there remains a wide unexplored domain. Alkyllithiums, which are often used as lithiating reagents, possess not only high basicity but also high nucleophilicity. This dual nature often results in side reactions when using alkyllithiums. Electron-excessive heteroaromatics are relatively stable to nucleophiles, so they can be lithiated using alkyllithium to give the lithio compound without any side reactions. By contrast, because electron-deficient heteroaromatics are generally reactive to nucleophiles and because the halogeno group acts as a good leaving group, treatment of electron-deficient haloheteroaromatics with alkyllithium proceeds with some side reactions. Hence, there are few reports on the selective lithiation of electron-deficient heteroaromatics. For example, it has been reported that 7-iodo-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine is lithiated at the 7-position,[3] but this reaction requires a temperature of −100°C, and gives the corresponding products in low yield. Similarly, the reaction of 4-iodo-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine with *n*-butyllithium in THF at −78°C gave multispots in thin layer chromatography.

Recently, lithiation via a tellurium–lithium exchange reaction has been reported.[4–6] As the rate of the tellurium–lithium exchange reaction is much faster than that of the halogen–lithium exchange reaction, the former reaction is expected to be useful for the lithiation of electron-deficient heteroaromatics. Lithiation of electron-deficient heteroaromatics, using the lithium–tellurium exchange reaction, has not been studied systematically except for the lithiation of a pyridine derivative.[7] Hence, investigations were performed aimed at establishing the feasibility of introducing an electrophile into easily accessible electron-deficient heteroaromatics. As a study of the lithiation of 4-chloro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine has previously been reported by us,[8] we applied similar methods to the lithiation of some electron-deficient haloheteroaromatics in this work.

## 2. Results and discussion

Reaction of 4-chloro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**1**) with lithium *n*-butanetellurolate, obtained from the reaction of tellurium and *n*-butyllithium, proceeded smoothly at rt to give *n*-butyl 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl telluride (**2**) in 90% yield. Subsequently, **2** was converted into the product **4** in 52% yield using



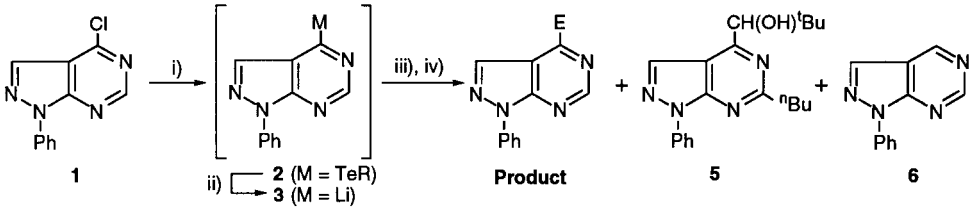

**Scheme 1.** Reagents and conditions: (i) $^{n}$BuLi (1.1 equiv.)/− 78°C; (ii) $^{t}$BuCH=O (5.0 equiv.)/− 78°C to rt; (iii) $H_3O^+$/rt.

*Keywords*: lithiation; tellurium and compounds; heteroaromatics.

* Corresponding author. Tel.: +81-54-264-5542; fax: +81-54-264-5099; e-mail: tanji@smail.u-shizuoka-ken.ac.jp

0040–4020/01/$ - see front matter 
PII: S0040-4020(01)00089-8

**Table 1.** Reagents and conditions: (i) RTeLi (1.1 equiv.)/THF/rt; (ii) RLi/−78°C/time; (iii) electrophile (5.0 equiv.)/− 78°C to rt; (iv) $H_3O^+$/rt



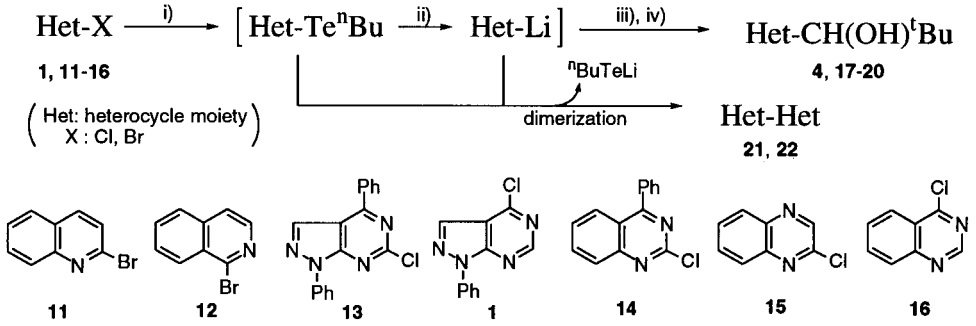

| Entry | Lithiation condition | | Electrophile | –E | Yield (%) | | |
|---|---|---|---|---|---|---|---|
| | RLi | Time (min) | | | Product | **5** | **6** |
| 1 | $^n$BuLi (1.1 equiv.) | 10 | $^t$BuCH=O | –CH(OH)$^t$Bu | 74 (**4**) | | |
| 2 | $^n$BuLi (1.1 equiv.) | 90 | $^t$BuCH=O | –CH(OH)$^t$Bu | 50 (**4**) | | |
| 3 | $^n$BuLi (3.0 equiv.) | 10 | $^t$BuCH=O | –CH(OH)$^t$Bu | 43 (**4**) | 14 | |
| 4 | MeLi (1.1 equiv.) | 10 | $^t$BuCH=O | –CH(OH)$^t$Bu | 48 (**4**) | | |
| 5 | PhLi (1.1 equiv.) | 10 | $^t$BuCH=O | –CH(OH)$^t$Bu | 16 (**4**) | | |
| 6 | $^n$BuLi (1.1 equiv.) | 10 | PhCH=O | –CH(OH)Ph | 61 (**7**) | | |
| 7 | $^n$BuLi (1.1 equiv.) | 10 | $Ph_2C$=O | –C(OH)$Ph_2$ | 82 (**8**) | | |
| 8 | $^n$BuLi (1.1 equiv.) | 10 | $Me_2C$=O | –C(OH)$Me_2$ | 68 (**9**) | | 3 |
| 9 | $^n$BuLi (1.1 equiv.) | 10 | MeCOCH=$CH_2$ | –CMe(OH)CH=$CH_2$ | 48 (**10**) | | 23 |

*n*-butyllithium and pivalaldehyde at −78°C (Scheme 1). The high rate of the tellurium–lithium exchange reaction and the low ability of the *n*-butyltelluro group as a leaving group seems to be the reason for the ease of lithiation of **2**. Thus, our method using the tellurium–lithium exchange reaction even enables the conversion of the chloro compound, which is not usually active in the halogen–lithium exchange reaction, into the lithio adduct.

As it was found that the telluride **2** was obtained in excellent yield, the one-pot lithiation without intermdiate isolation of the telluride **2** was then carried out (Table 1). The conditions shown in entry 1 of the table gave the product **4** in good yield. When the lithiating time was extended to 90 min, the yield of the product **4** showed a slight decline. Hence it appears that, even at a reaction temperature of −78°C, the 4-lithio derivative **3** is unstable. It should be noted that treatment of **2**, generated in situ from **1**, with an excess of *n*-butyllithium gives the product **5**, which is derived from the nucleophilic attack of *n*-butyllithium at the 6-position of the 4-lithio derivative **3** (entry 3). Using methyllithium or phenyllithium instead of *n*-butyllithium, we found that the nature of the alkyllithium affects the yield of the product **4**. The introduction of some electrophiles at the 4-position in 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine was accomplished in good to fair yields under the best conditions we examined (entries 6–9). When ketones having α-hydrogens were used in this reaction, the protonated compound **6** was obtained (entry 8,9).

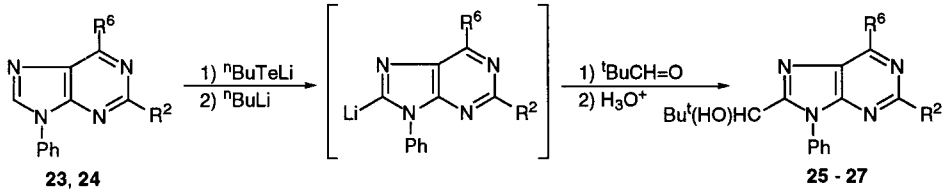
Next, lithiation of some electron-deficient heteroaromatics shown in Table 2 was carried out. Although the introduction of an electrophile was accomplished when 2-bromoquinoline (**11**), 1-bromoisoquinoline (**12**), 6-chloro-1,4-diphenyl-

**Table 2.** Reagents and conditions: (i) $^n$BuTeLi (1.1 equiv.)/THF; (ii) $^n$BuLi (1.1 equiv.)/− 78°C; (iii) pivalaldehyde (5.0 equiv.)/− 78°C to rt; (iv) $H_3O^+$/rt




| Entry | Substrate | Yield (%) | |
|---|---|---|---|
| | | Het–CH(OH)$^t$Bu | Het–Het |
| 1 | 2-bromoquinoline (**11**) | 75 (**17**) | |
| 2 | 1-bromoisoquinoline (**12**) | 36 (**18**) | |
| 3 | 6-chloro-1,4-diphenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**13**) | 52 (**19**) | |
| 4 | 4-chloro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**1**) | 74 (**4**) | |
| 5 | 2-chloro-4-phenylquinazoline (**14**) | 63 (**20**) | |
| 6 | 2-chloroquinoxaline (**15**) | | 36 (**21**) |
| 7 | 4-chloroquinazoline (**16**) | | 94 (**22**) |

**Table 3.**




**23, 24** **25 - 27**

| Entry | Substrate | Yield (%) |
|---|---|---|
| 1 | **23** ($R^2$=Me, $R^6$=Cl) | 37 (**25**: $R^2$=Me, $R^6$=H), 29 (**26**: $R^2$=CH(OH)$^t$Bu) |
| 2 | **24** ($R^2$=Cl, $R^6$=H) | 34 (**27**: $R^2$=$R^6$=H) |

1*H*-pyrazolo[3,4-*d*]pyrimidine (**13**), 4-chloro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**1**) or 2-chloro-4-phenyl-quinazoli-ne (**14**) was used, dimerization occurred when 2-chloroquinoxaline (**15**) or 4-chloroquina-zoline (**16**) acted as substrate. It can be estimated that the extent of dimerization depends on the reactivities of the telluride as an electrophile and the lithio derivative as a nucleophile. As the 4-position of quinazoline or the 2-position of quinoxaline is highly reactive[9] with nucleophiles, such as carbanions, amines or alkoxides, dimerization occurred when **15** or **16** was used as a substrate. The 2-position of quinazoline has a similar reactivity to that of the 2-position of quinoxaline; however, interestingly dimerization does not occur. We surmise that the 2-carbanion of quinazoline is stabilized by the electron withdrawing effect of the two ring nitrogens.

Lithiation of 9-phenyl-9*H*-purine derivatives (**23**,**24**) took place with 8-lithiation to give the 8- (**25**,**27**) and 6,8- (**26**) substituted products (Table 3). A similar relocation of the carbanion was reported by Leonard.[10]

Lithiation at the 8-position could occur by two main routes. One would involve hydrogen abstraction at the 8-position of the 6-carbanion, formed via the tellurium–lithium exchange reaction, by another 6-carbanion then, the resulting 6,8-dilithio derivative may abstract hydrogen at the 8-position from the 6-protonated derivative. Another route would involve the direct lithiation at the 8-position of the 6-carbanion by *n*-butyllithium (Scheme 2).

## 3. Conclusion

On examining the lithiation of electron-deficient heteroaromatics using the tellurium–lithium exchange reaction, we observed the following (these reactions can be divided broadly into three patterns):

1. Since the rate of tellurium–lithium exchange reaction is so fast, many electron-deficient heteroaromatic tellurides react selectively with 1 equiv. of *n*-butyllithium to give the corresponding lithio derivatives.
2. When the tellurium-substituted position at heterocycles has a high reactivity towards nucleophiles, the lithio derivative reacts with the unreacted telluride to give the corresponding dimer. The kind of reaction pattern depends on the position of tellurium-substitution in the heterocycle. For example, 2-quinazolinyl tellurides gives 2-lithioquinazolines selectively, while 4-quinazolinyl tellurides gives the 4,4′-dimer.
3. The presence of an acidic proton (e.g. the 8-position of 9*H*-purines) causes relocation of the carbanion.

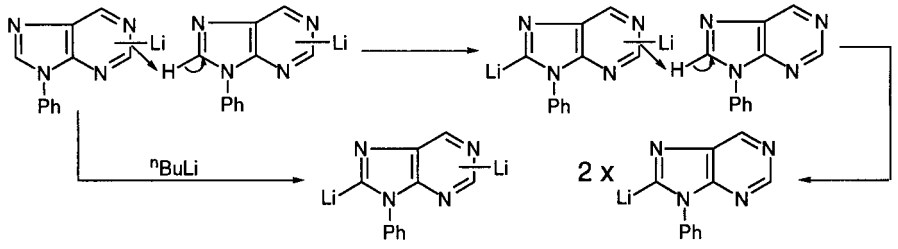
We postulate that same scheme might be applied to many heterocycles as yet not researched by us.

## 4. Experimental

### 4.1. General

Melting points were not corrected. $^1$H NMR spectra were measured with HITACHI R-90H spectrometer using TMS as an internal standard.

**4.1.1. Synthesis of *n*-butyl 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl telluride (2).** In a three-necked round-bottomed flask, a suspension of 281 mg (2.20 mmol) of tellurium in 30 ml of THF was treated dropwise with 1.58 ml (1.39 M, 2.20 mmol) of *n*-butyllithium while stirring at rt. As the *n*-butyllithium was added, the tellurium dissolved and the reaction mixture turned dark. The solution became colorless near the equivalence point. After stirring the reaction mixture for 10 min, a solution of 461 mg (2.00 mmol) of 4-chloro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyri-




**Scheme 2.**

| Entry | Alkyllithium (equiv.) | Lithiation time (min) | Product in mg (yield in %) | |
|---|---|---|---|---|
| | | | **4** | **5** |
| 1 | $^n$BuLi (1.1) | 10 | 418 (74) | |
| 2 | $^n$BuLi (1.1) | 90 | 281 (50) | |
| 3 | $^n$BuLi (3.0) | 10 | 237 (43) | 97 (14) |
| 4 | MeLi (1.1) | 10 | 273 (48) | |
| 5 | PhLi (1.1) | 10 | 90 (16) | |

midine (**1**) in 12 ml of THF was added and stirred for 10 min. 50 ml of water was added and neutralized with 1N HCl. The mixture was extracted with ethyl acetate and dried over $Na_2SO_4$. The solvent was removed by rotary evaporation, and residual crude product purified with $SiO_2$ chromatography (eluted with hexane–ethyl acetate (10:1)) to give 684 mg (90%) of *n*-butyl 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl telluride (**2**). Pale-green solids. $^1$H NMR ($CDCl_3$); ppm: 0.97 (3H, t, $J$=6.9 Hz, $-CH_2CH_2CH_2CH_3$), 1.13–1.67 (2H, m, $-CH_2CH_2CH_2CH_3$), 1.67–2.16 (2H, m, $-CH_2CH_2CH_2CH_3$), 3.43 (2H, t, $J$=7.3 Hz, $-CH_2CH_2CH_2CH_3$), 7.25–7.67 (3H, m, phenyl-H), 8.08 (1H, s, C$^3$–H), 8.10–8.31 (2H, m, phenyl-H), 8.77 (1H, s, C$^6$–H); Anal. calcd for $C_{15}H_{16}N_4Te$: C, 47.42; H, 4.24; N, 14.75. Found: C, 47.53; H, 4.03; N, 14.47.

**4.1.2. Lithiation of 2.** In a three-necked round-bottomed flask, a solution of 760 mg (2.00 mmol) of **2** in 30 ml of THF was treated with 1.58 ml (1.39 M, 2.20 mmol) of *n*-butyllithium in one portion while being stirred at an interior temperature of −78°C. The mixture was stirred for 10 min then 861 mg (10.0 mmol) of pivalaldehyde was added. The reaction mixture was then warmed to rt and 50 ml of water was added, and neutralized with 1N HCl. The mixture was extracted with ethyl acetate and dried over $Na_2SO_4$. The solvent was removed by a rotary evaporator, and the residual crude product was purified with $SiO_2$ chromatography (eluted with hexane–ethyl acetate (2:1)) to give 294 mg (52%) of 2,2-dimethyl-1-(1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)-1-propanol (**4**). Pale-yellow prisms (recryst. from hexane–ethyl acetate). Mp 125–126°C. $^1$H NMR ($CDCl_3$); ppm: 1.04 (9H, s, $C(CH_3)_3$), 3.70 (1H, d, $J$=6.8 Hz, –OH), 4.78 (1H, d, $J$=6.8 Hz, –CH–), 7.26–7.70 (3H, m, phenyl-H), 8.00–8.35 (2H, m, phenyl-H), 8.36 (1H, s, C$^3$–H), 9.05 (1H, s, C$^6$–H); Anal. calcd for $C_{16}H_{18}N_4O$: C, 68.06; H, 6.43; N, 19.84. Found: C, 67.87; H, 6.38; N, 20.02.

**4.1.3. Lithiation of 2 generated in situ from 1.** In a three-necked round-bottomed flask, a suspension of tellurium (2.20 mmol) in THF (30 ml) was treated dropwise with alkyllithium (2.20 mmol) while stirring at rt. As alkyllithium was added, tellurium was dissolved and the reaction mixture turned dark. This change of color proved the equation of the amount of alkyllithium. This change of color confirmed the supposed stoichiometry. After stirring the reaction mixture for10 min, a solution of **1** (2.00 mmol) in THF (12 ml) was added and stirred at an appropriate temperature. The mixture was cooled to −78°C then treated with alkyllithium (molar: shown in Table 4) in one portion while being stirred at an interior temperature of −78°C. The mixture was stirred for the time shown below then, electrophile (10.0 mmol) was added. The reaction mixture was then warmed to rt, and 50 ml of water was added, and neutralized with 1N HCl. The mixture was extracted with ethyl acetate and dried over $Na_2SO_4$. The solvent was removed by a rotary evaporator, and the residual crude product was purified with $SiO_2$ chromatography.

**4.1.4. 2,2-Dimethyl-1-(6-*n*-butyl-1-phenyl-1*H*-pyrazolo-[3,4-*d*]pyrimidin-4-yl)-1-propanol (5).** Pale-yellow oil. $^1$H NMR ($CDCl_3$); ppm: 0.77–1.15 (12H, m, $^t$Bu and $CH_2CH_2CH_2CH_3$), 1.15–1.64 (2H, m, $CH_2CH_2CH_2CH_3$), 1.64–2.08 (2H, m, $CH_2CH_2CH_2CH_3$), 3.09 (2H, t, $J$=7.5 Hz, $CH_2CH_2CH_2CH_3$), 4.05 (1H, d, $J$=7.3 Hz, –OH), 4.73 (1H, d, $J$=7.3 Hz, –CH–), 7.27–7.68 (3H, m, phenyl-H), 8.14–8.41 (2H, m, phenyl-H), 8.23 (1H, s, C$^3$–H). Anal. calcd for $C_{20}H_{26}N_4O$: C, 70.98; H, 7.74; N, 16.55. Found: C, 71.01; H, 7.74; N, 16.52.

**4.1.5. Lithiation of some haloheteroarenes: general procedure.** A solution of starting material in THF was added to the solution of *n*-butanetellurolate in THF at condition. The mixture was cooled to −78°C, treated with *n*-butyllithium in one portion. The mixture was stirred for 10 min then, electrophile was added. The reaction mixture was then warmed to rt, water was added, and neutralized with 1N HCl. The mixture was extracted with ethyl acetate and dried over $Na_2SO_4$. The solvent was removed by a rotary evaporator, and the residual crude product was purified with $SiO_2$ chromatography.

**4.1.6. Phenyl(1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)methanol (7).** Lithium *n*-butanetellurolate (2.20 mmol), **1** 461 mg (2.00 mmol), *n*-butyllithium (2.20 mmol) and benzaldehyde 1061 mg (10.0 mmol) were used in this reaction to give 370 mg (yield: 61%) of the compound[11] according to the protocol described in general procedure (condition: rt/10 min). White solids. Mp 103–104°C (lit. 107–110°C). $^1$H NMR ($CDCl_3$); ppm: 4.78 (1H, d, $J$=3.8 Hz, –OH), 6.08 (1H, d, $J$=3.8 Hz, –CH–), 7.26–7.68 (8H, m, phenyl-H), 8.01 (1H, s, C$^3$–H), 8.03–8.30 (2H, m, phenyl-H), 9.07 (1H, s, C$^6$–H).

**4.1.7. Diphenyl(1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)methanol (8).** Lithium *n*-butanetellurolate (2.20 mmol), **1** 461 mg (2.00 mmol), *n*-butyllithium (2.20 mmol) and benzophenone 1822 mg (10.0 mmol) were used in this reaction to give 624 mg (yield: 82%) of the compound according to the protocol described in general procedure (condition: rt/10 min). White needles (recryst. from hexane–ethyl acetate). Mp 219–221°C. $^1$H NMR (DMSO-$d_6$); ppm: 7.15–7.80 (13H, m, aromatic-H), 8.06–8.30 (2H, m, aromatic-H), 8.53 (1H, s, C$^3$–H), 9.05 (1H, s, C$^6$–H). Anal. calcd for $C_{24}H_{18}N_4O$: C, 76.17; H, 4.79; N, 14.81. Found: C, 76.23; H, 4.82; N, 14.64.

**4.1.8. 2-(1-Phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)-2-**

**propanol (9)**Lithium *n*-butanetellurolate (2.20 mmol), **1** 461 mg (2.00 mmol), *n*-butyllithium (2.20 mmol) and acetone 580 mg (10.0 mmol) were used in this reaction to give 344 mg (yield: 68%) of the compound and 12 mg (yield: 3%) of **6**[12] according to the protocol described in general procedure (condition: rt/10 min). Yellow prisms (recryst. from hexane–ethyl acetate). Mp 75°C. $^1$H NMR ($CDCl_3$); ppm: 1.76 (6H, s, $(CH_3)_2$), 4.33 (1H, s, –OH), 7.32–7.77 (3H, m, phenyl-H), 8.12–8.40 (2H, m, phenyl-H), 8.47 (1H, s, $C^3$–H), 9.03 (1H, s, $C^6$–H). Anal. calcd for $C_{14}H_{14}N_4O$: C, 66.13; H, 5.55; N, 22.03. Found: C, 66.12; H, 5.38; N, 21.86.

**4.1.9. 1-Phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (6).** Lithium *n*-butanetellurolate (2.20 mmol), **1** 461 mg (2.00 mmol), *n*-butyllithium (2.20 mmol) and acetone 580 mg (10.0 mmol) were used in this reaction to give 12 mg (yield: 3%) of the compound[12] and 344 mg (yield: 68%) of **9** according to the protocol described in general procedure (condition: rt/10 min). Pale-yellow solids. Mp 80°C (lit. 79–81°C). $^1$H NMR ($CDCl_3$); ppm: 7.30–7.70 (3H, m, phenyl-H), 8.11–8.40 (2H, m, phenyl-H), 8.32 (1H, s, $C^3$–H), 9.13 (1H, s, $C^6$–H), 9.27 (1H, s, $C^4$–H).

**4.1.10. 2-(1-Phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)-3-buten-2-ol (10).** Lithium *n*-butanetellurolate (2.20 mmol), **1** 461 mg (2.00 mmol), *n*-butyllithium (2.20 mmol) and 3-buten-2-one 700 mg (10.0 mmol) were used in this reaction to give 255 mg (yield: 48%) of the compound and 90 mg (yield: 23%) of **6** according to the protocol described in general procedure (condition: rt/10 min). White powder (recryst. from hexane–ethyl acetate). Mp 65–66°C. $^1$H NMR ($CDCl_3$); ppm: 1.84 (3H, s, $CH_3$), 4.63 (1H, s, –OH), 5.28 (1H, dd, $J$=10.4, 0.9 Hz, alkene-H), 5.56 (1H, dd, $J$=17.1, 0.9 Hz, alkene-H), 6.33 (1H, dd, $J$=17.1, 10.4 Hz, alkene-H), 7.31–7.71 (3H, m, phenyl-H), 8.12–8.33 (2H, m, phenyl-H), 8.44 (1H, s, $C^3$–H), 9.03 (1H, s, $C^6$–H); Anal. calcd for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04. Found: C, 67.51; H, 5.30; N, 20.78.

**4.1.11. 2,2-Dimethyl-1-(2-quinolinyl)-1-propanol (17).** Lithium *n*-butanetellurolate (2.20 mmol), 2-bromoquinoline (**11**) 416 mg (2.00 mmol), *n*-butyllithium (2.20 mmol) and pivalaldehyde 861 mg (10.0 mmol) were used in this reaction to give 323 mg (yield: 75%) of the compound according to the protocol described in general procedure (condition: reflux/43 h). Pale-yellow plates (recryst. from hexane–ethyl acetate). Mp 73–75°C. $^1$H NMR ($CDCl_3$); ppm: 0.98 (9H, s, $^t$Bu), 4.20–5.10 (1H, br, –OH), 4.53 (1H, brs, –CH–), 7.14–7.95 (4H, m, aromatic-H), 8.09 (2H, d, $J$=8.4 Hz, aromatic-H); Anal. calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.00; H, 7.99; N, 6.58.

**4.1.12. 2,2-Dimethyl-1-(1-isoquinolinyl)-1-propanol (18).** Lithium *n*-butanetellurolate (2.20 mmol), 1-bromoisoquinoline (**12**) 320 mg (1.54 mmol), *n*-butyllithium (1.69 mmol) and pivalaldehyde 662 mg (7.69 mmol) were used in this reaction to give 118 mg (yield: 36%) of the compound and 75 mg (yield: 38%) of isoquinoline according to the protocol described in general procedure (condition: reflux/24 h). White needles (recryst. from hexane). Mp 106–107°C. $^1$H NMR ($CDCl_3$); ppm: 0.95 (9H, s, $^t$Bu), 4. 50 (1H, d, $J$=8.8 Hz, –OH), 5.26 (1H, d, $J$=8.8 Hz, –CH–), 7.42–7.97 (4H, m, aromatic-H), 8.06–8.31 (1H, m, aromatic-H), 8.50 (1H, d, $J$=5.7 Hz, aromatic-H); Anal. calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.12; H, 7.83; N, 6.54.

**4.1.13. 2,2-Dimethyl-1-(1,4-diphenyl-1*H*-pyrazolo[3,4-*d*]-pyrimidin-6-yl)-1-propanol (19).** Lithium *n*-butanetellurolate (2.20 mmol), 6-chloro-1,4-diphenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**13**) 614 mg (2.00 mmol), *n*-butyllithium (2.20 mmol) and pivalaldehyde 861 mg (10.0 mmol) were used in this reaction to give 370 mg (yield: 52%) of the compound according to the protocol described in general procedure (condition: rt/10 min). Pale-yellow needles (recryst. from hexane–ethyl acetate). Mp 158°C. $^1$H NMR ($CDCl_3$); ppm: 1.07 (9H, s, $^t$Bu), 4.29 (1H, d, $J$=7.7 Hz, –OH), 4.68 (1H, d, $J$=7.7 Hz, –CH–), 7.26–7.75 (6H, m, phenyl-H), 8.09–8.37 (4H, m, phenyl-H), 8.52 (1H, s, $C^3$–H). Anal. calcd for $C_{22}H_{22}N_4O$: C, 73.72; H, 6.19; N, 15.63. Found: C, 73.84; H, 6.36; N, 15.48.

**4.1.14. 2,2-Dimethyl-1-(4-phenylquinazolin-2-yl)-1-propanol (20).** Lithium *n*-butanetellurolate (2.20 mmol), 2-chloro-4-phenylquinazoline (**14**) 481 mg (2.00 mmol), *n*-butyllithium (2.20 mmol), and pivalaldehyde 861 mg (10.0 mmol) were used in this reaction to give 366 mg (yield: 63%) of the compound according to the protocol described in general procedure (condition: rt/10 min). White needles (recryst. from hexane–ethyl acetate). Mp 120–121°C. $^1$H NMR ($CDCl_3$); ppm: 1.05 (9H, s, $^t$Bu), 4.42 (1H, d, $J$=7.7 Hz, –OH), 4.72 (1H, d, $J$=7.7 Hz, –CH–), 7.40–8.24 (9H, m, aromatic-H); Anal. calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58. Found: C, 78.00; H, 6.90; N, 9.66.

**4.1.15. 2,2′-Biquinoxalinyl (21).** Lithium *n*-butanetellurolate (2.20 mmol), 2-chloroquinoxaline (**15**) 329 mg (2.00 mmol), *n*-butyllithium (2.20 mmol) and pivalaldehyde 861 mg (10.0 mmol) were used in this reaction to give 95 mg (yield: 36%) of the compound[13] according to the protocol described in general procedure (condition: rt/10 min). Dark-red solids. Mp 272°C (lit. 274°C). $^1$H NMR ($CDCl_3$); ppm: 7.76–8.06 (4H, m, aromatic-H), 8.11–8.42 (4H, m, aromatic-H), 10.13 (2H, s, $C^3$ and $C^{3'}$–H).

**4.1.16. 4,4′-Biquinazolinyl (22).** Lithium *n*-butanetellurolate (2.20 mmol), 4-chloroquinazoline (**16**) 329 mg (2.00 mmol), *n*-butyllithium (2.20 mmol) and pivalaldehyde 861 mg (10.0 mmol) were used in this reaction to give 240 mg (yield: 94%) of the compound[14] according to the protocol described in general procedure (condition: rt/10 min). White solids. Mp 210–212°C (lit. 208–209°C). $^1$H NMR ($CDCl_3$); ppm: 7.50–7.83 (2H, m, $C^6$ and $C^{6'}$–H), 7.83–8.17 (4H, m, $C^5$, $C^7$, $C^{5'}$ and $C^{7'}$–H), 8.17–8.42 (2H, m, $C^8$ and $C^{8'}$–H), 9.54 (2H, s, $C^2$ and $C^{2'}$–H).

**4.1.17. 2,2-Dimethyl-1-(2-methyl-9-phenyl-9*H*-purin-8-yl)-1-propanol (25).** Lithium *n*-butanetellurolate (1.10 mmol), 6-chloro-2-methyl-9-phenyl-9*H*-purine (**23**) 245 mg (1.00 mmol), *n*-butyllithium (1.10 mmol) and pivalaldehyde 431 mg (5.00 mmol) were used in this reaction to give 110 mg (yield: 37%) of the compound and 111 mg (yield: 29%) of **26** according to the protocol described in general procedure (condition: rt/30 min). Pale-yellow powder (recryst. from hexane–ethyl acetate). Mp

186°C. $^1$H NMR ($CDCl_3$); ppm: 0.90 (9H, s, $^t$Bu), 2.75 (3H, s, $CH_3$), 3.09 (1H, d, $J$=9.7 Hz, –OH), 4.56 (1H, d, $J$=9.7 Hz, –CH–), 7.28–7.75 (5H, m, phenyl-H), 9.06 (1H, s, $C^6$–H). Anal. calcd for $C_{17}H_{20}N_4O$: C, 68.89; H, 6.80; N, 18.90. Found: C, 69.12; H, 6.71; N, 18.74.

**4.1.18. 6,8-Bis(1-hydroxy-2,2-dimethylpropyl)-2-methyl-9-phenyl-9*H*-purine (26).** Lithium *n*-butanetellurolate (1.10 mmol), 6-chloro-2-methyl-9-phenyl-9*H*-purine (**23**) 245 mg (1.00 mmol), *n*-butyllithium (1.10 mmol) and pivalaldehyde 431 mg (5.00 mmol) were used in this reaction to give 111 mg (yield: 29%) of the compound and 110 mg (yield: 37%) of **25** according to the protocol described in general procedure (condition: rt/30 min). Pale-yellow prisms (recryst. from hexane). Mp 176–179°C. $^1$H NMR ($CDCl_3$); ppm: 0.87 (9H, s, $^t$Bu), 1.03 (9H, s, $^t$Bu), 2.72 (3H, s, $CH_3$), 2.90 (1H, dd, $J$=9.8, 5.6 Hz, –OH), 4.30–4.60 (2H, m, –CH– and –OH), 4.96 (1H, t, $J$=8.8 Hz, –CH–), 7.30–7.67 (5H, m, phenyl-H). Anal. calcd for $C_{22}H_{30}N_4O_2$: C, 69.08; H,7.91; N, 14.65. Found: C, 69.12; H, 7.85; N, 14.54.

**4.1.19. 2,2-Dimethyl-1-(9-phenyl-9*H*-purin-8-yl)-1-propanol (27).** Lithium *n*-butanetellurolate (2.20 mmol), 2-chloro-9-phenyl-9*H*-purine (**24**) 461 mg (2.00 mmol), *n*-butyllithium (2.20 mmol) and pivalaldehyde 861 mg (10.0 mmol) were used in this reaction to give 190 mg (yield: 34%) of 111 mg (yield: 29%) of the compound according to the protocol described in general procedure (condition: rt/2 h). Pale-yellow needles (recryst. from hexane–ethyl acetate). Mp 164°C. $^1$H NMR ($CDCl_3$); ppm: 0.92 (9H, s, $^t$Bu), 3.08 (1H, d, $J$=9.7 Hz, –OH), 4.60 (1H, d, $J$=9.7 Hz, –CH), 7.31–7.74 (5H, m, phenyl-H), 8.95 (1H, s, $C^2$–H), 9.18 (1H, s, $C^6$–H). Anal. calcd for $C_{16}H_{18}N_4O$: C, 68.06; H, 6.43; N, 19.84. Found: C, 68.08; H, 6.35; N, 19.61.

## References


1. Queguiner, G.; Marsais, F.; Snieckus, V.; Epsztajn, J. *Adv. Heterocycl. Chem.* **1991**, *52*, 187–304.
2. Rewcastle, G. W.; Katritzky, A. R. *Adv. Heterocycl. Chem.* **1993**, *56*, 155–302.
3. Tanji, K.; Kato, H.; Higashino, T. *Chem. Pharm. Bull.* **1991**, *39*, 2793–2796.
4. Hiiro, T.; Morita, Y.; Inoue, T.; Kambe, N.; Ogawa, A.; Ryu, I.; Sonoda, N. *J. Am. Chem. Soc.* **1990**, *112*, 455–457.
5. Hiiro, T.; Kambe, N.; Ogawa, A.; Miyoshi, N.; Murai, S.; Sonoda, N. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1187–1188.
6. Hiiro, T.; Mogami, T.; Kambe, N.; Fujiwara, S.; Sonoda, N. *Synth. Commun.* **1990**, *20*, 703–711.
7. Kondo, Y.; Shilai, M.; Uchiyama, M.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1781–1782.
8. Sugimoto, O.; Sudo, M.; Tanji, K. *Tetrahedron Lett.* **1999**, *40*, 2139–2140.
9. Chapman, N. B.; Russell-Hill, D. Q. *J. Chem. Soc.* **1956**, 1563–1572.
10. Leonard, N. J.; Bryant, J. D. *J. Org. Chem.* **1979**, *44*, 4612–4616.
11. Higashino, T.; Goi, M.; Hayashi, E. *Chem. Pharm. Bull.* **1976**, *24*, 238–252.
12. Higashino, T.; Iwai, Y.; Hayashi, E. *Yakugaku Zasshi* **1974**, *94*, 666–671.
13. Maurer, K.; Boettger, B. *Chem. Ber.* **1938**, *71*, 2092–2094.
14. Higashino, T. *Chem. Pharm. Bull.* **1962**, *10*, 1043–1047.