HETEROCYCLES, Vol. 57, No. 2, 2002, pp. 323-326, Received, 7th November, 2001

PREPARATION OF A USEFUL SYNTHETIC PRECURSOR, 2-SUBSTITUTED 4(3*H*)-QUINAZOLINONE: DIRECTED LITHIATION AND N^3-DEPROTECTION OF 3-*t*-BUTOXYCARBONYL-4(3*H*)-QUINAZOLINONE

Osamu Sugimoto,* Yasuhiro Yamauchi, and Ken-ichi Tanji*

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

Abstract – Directed lithiation of 3-*t*-butoxycarbonyl-4(3*H*)-quinazolinone using LDA was accomplished to afford 2-substituted 3-*t*-butoxycarbonyl-4(3*H*)-quinazolinones. The *t*-butoxycarbonyl group of these products was easily deprotected to give key intermediates for the synthesis of quinazoline derivatives, 2-substituted 4(3*H*)-quinazolinones, in good yield.

INTRODUCTION

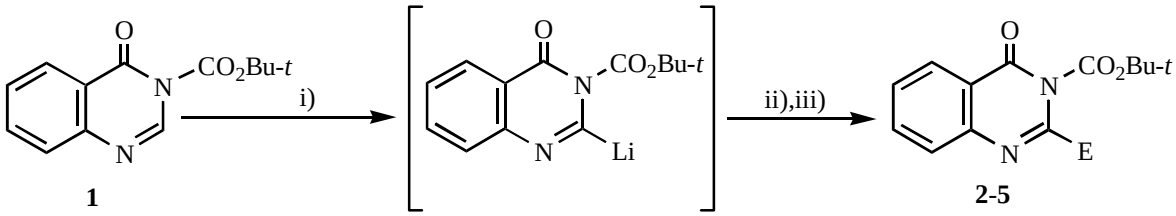
Fused pyrimidinones (fused hydroxypyrimidines) are well known as substrates for the synthesis of fused halogenopyrimidines. Fused pyrimidinones react with phosphorus oxyhalide,[1] phosphorus pentahalide,[2] or triphenylphosphine / *N*-halogenosuccinimide[3] to give the corresponding fused halogenopyrimidines. Recently, directed lithiation (hydrogen-lithium exchange reaction) of N^3-protected 4(3*H*)-quinazolinone was reported by Smith, *et al.*[4] This is a useful method for the introduction of an electrophilic substituent into 4(3*H*)-quinazolinones, but it is difficult to convert the product, 2-substituted 4(3*H*)-quinazolinones, into 2-substituted quinazolines because deprotection of the N^3-acylamino group is difficult. In this paper, a synthetic route to 2-substituted 4(3*H*)-quinazolinones aimed at their conversion into 2-substituted quinazolines is demonstrated.

RESULTS AND DISCUSSION

At first, directed lithiation of 4(3*H*)-quinazolinone was attempted, but only the starting material was recovered when lithium diisopropylamide (LDA) or lithium 2,2,6,6-tetramethylpiperidide (LTMP) was used as a lithiating reagent. These results would indicate that lithium amides such as LDA or LTMP have insufficient reactivity to effect dilithiation of an aromatic ring to give the dilithio intermediate. When *n*-butyllithium was used, 2-*n*-butyl-2,3-dihydro-4(1*H*)-quinazolinone was obtained in 40% yield

by the undesirable reaction of a nucleophilic attack by *n*-butyllithium at the 2-position of the substrate. From these results, directed lithiation of N^3-protected 4(3*H*)-quinazolinones was planned. The *t*-butoxycarbonyl group was expected to be favorable for the N^3-protection of 4(3*H*)-quinazolinone because the *N*-*t*-butoxycarbonyl group can be readily deprotected by acids. As shown in Table 1, directed lithiation of 3-*t*-butoxycarbonyl-4(3*H*)-quinazolinone (**1**) was carried out. The use of *n*-butyllithium or LTMP followed by addition of pivalaldehyde gave the desired product (**2**) in 5%, 19% yield, respectively (Entries 1,2). When 1.0-2.0 equivalent(s) of LDA was used, the product (**2**) was obtained in 35% yield (Entries 3,4). Next, directed lithiation of **1** using a stoichiometric amount of LDA followed by addition of a variety of carbonyl compounds (benzaldehyde, acetone, and cyclohexanone) was undertaken to afford the corresponding products (**3**-**5**) in moderate yields. The structure of **2**-**5** was identified by the disappearance of the C^2-proton signal at ^{1}H-NMR and elemental analysis.

Table 1. Directed lithiation of 3-*t*-butoxycarbonyl-4(3*H*)-quinazolinone

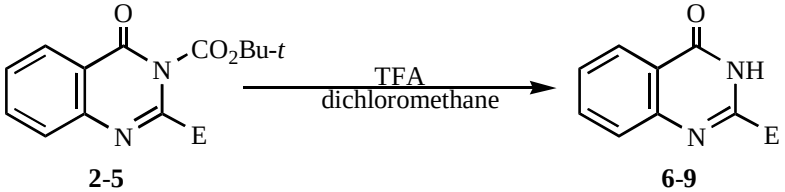


Reagents and conditions: i) Lithiating reagent / THF / -78 ^{o}C, 10 min; ii) Electrophile; iii) H_3O^+.

Entry	Lithiating reagent	Electrophile	-E (Product)	Yield (%)	Entry	Lithiating reagent	Electrophile	-E (Product)	Yield (%)
1	*n*-BuLi (1.1 eq)	*t*-BuCH=O	-CH(OH)Bu-*t* (**2**)	5	5	LDA (1.0 eq)	PhCH=O	-CH(OH)Ph (**3**)	42
2	LTMP (2.0 eq)	*t*-BuCH=O	-CH(OH)Bu-*t* (**2**)	19	6	LDA (1.0 eq)	Me_2C=O	-C(OH)Me_2 (**4**)	42
3	LDA (1.0 eq)	*t*-BuCH=O	-CH(OH)Bu-*t* (**2**)	35	7	LDA (1.0 eq)	C_5H_{10}C=O	-C(OH)C_5H_{10} (**5**)	48
4	LDA (2.0 eq)	*t*-BuCH=O	-CH(OH)Bu-*t* (**2**)	35					

The compounds (**2**-**5**) were deprotected to give the corresponding products (**6**-**9**) using trifluoroacetic acid in good yields as shown in Table 2. As the deprotected products (**6**-**9**) are expected to be converted by the method using some halogenating reagents[1-3] into 2-substituted 4-halogenoquinazolines, which would react with nucleophiles[5] to introduce nucleophilic substituents at the 4-position of quinazoline ring, this lithiation-deprotection method seems to be useful for the synthesis of quinazoline derivatives.

Table 2. Deprotection of N^3-*t*-butoxycarbonyl group of 4(3*H*)-quinazolinone derivatives



Entry	-E (Product)	Yield (%)
1	-CH(OH)Bu-*t* (**6**)	92
2	-CH(OH)Ph (**7**)	68
3	-C(OH)Me_2 (**8**)	76
4	-C(OH)C_5H_{10} (**9**)	91

In conclusion, we have accomplished a novel synthesis of 2-substituted 4(3*H*)-quinazolinones as a synthetic precursor of 2-substituted quinazolines using the directed lithiation and deprotection of the N^3-*t*-butoxycarbonyl group.

EXPERIMENTAL

All melting points were not corrected. ^{1}H-NMR spectra were measured with HITACHI R-90H spectrometer using TMS as an internal standard.

Synthesis of 3-*t*-butoxycarbonyl-4(3*H*)-quinazolinone (**1**): To a suspension of 4(3*H*)-quinazolinone (2923 mg, 20.0 mmol) in THF (250 mL), sodium hydride (60% in oil, 880 mg, 22.0 mmol) was added little by little and stirred for 2.5 h. A solution of di-*t*-butyl dicarbonate (6548 mg, 30.0 mmol) in THF (50 mL) was added to the mixture, stirred for further 45 min. The reaction mixture was quenched with water and extracted with ethyl acetate (400 mL). The organic layer was purified with silica gel chromatography (eluted with hexane-ethyl acetate (3:1)) to give **1** (3666 mg, 74%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) ppm: 1.66 (9H, *s*, OBu-*t*), 7.37-7.90 (3H, *m*, C^6, C^7 and C^8-H), 8.31 (1H, *dd*, J=7.1 Hz, 0.8 Hz, C^5-H), 8.45 (1H, *s*, C^2-H). *Anal.* Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.50; H, 5.73; N, 11.64.

Reaction of **1** with organolithiums (General procedure of Table 1): To a solution of **1** (498 mg, 2.00 mmol) in dry THF (30 mL), organolithium solution (2.00-4.00 mmol) was added dropwise so as to keep the inside temperature –78 ^{o}C and stirred for 10 min. Electrophile (10.0 mmol) was added and the mixture was raised to rt. The reaction mixture was quenched and neutralized with 1 *N* hydrochloric acid, extracted with ethyl acetate. The organic layer was purified with silica gel chromatography (Eluate: shown below) to give the corresponding product.

2,2-Dimethyl-1-(3-*t*-butoxycarbonyl-4(3*H*)-quinazolinon-2-yl)-1-propanol (**2**): White needles (recryst. from hexane-ethyl acetate). mp 191-192 ^{o}C. Eluate=hexane-ethyl acetate (4:1-1:1). ^{1}H-NMR ($CDCl_3$) ppm: 1.09 (9H, *s*, CBu-*t*), 1.47 (9H, *s*, OBu-*t*), 5.26 (1H, *s*, CH), 7.39-7.61 (1H, *m*, C^6-H), 7.65-7.93 (2H, *m*, C^7 and C^8-H), 8.31 (1H, *d*, J=7.7 Hz, C^5-H), 9.35 (1H, *br s*, OH). *Anal.* Calcd for $C_{18}H_{24}N_2O_4$: C, 65.04; H, 7.28; N, 8.43. Found: C, 64.97; H, 7.29; N, 8.57.

(3-*t*-Butoxycarbonyl-4(3*H*)-quinazolinon-2-yl)phenylmethanol (**3**): White powder (recryst. from hexane-ethyl acetate). mp 193 ^{o}C. Eluate=hexane-ethyl acetate (2:1-1:1). ^{1}H-NMR ($CDCl_3$) ppm: 1.47 (9H, *s*, OBu-*t*), 4.69 (1H, *s*, OH), 6.48 (1H, *s*, CH), 7.15-7.84 (8H, *m*, C^6, C^7, C^8 and phenyl-H), 8.27 (1H, *d*, J=7.7 Hz, C^5-H). *Anal.* Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.07; H, 5.74; N, 8.10.

2-(3-*t*-Butoxycarbonyl-4(3*H*)-quinazolinon-2-yl)-2-propanol (**4**): White plates (recryst. from hexane-ethyl acetate). mp 144-146 ^{o}C. Eluate=hexane-ethyl acetate (2:1-1:1). ^{1}H-NMR ($CDCl_3$) ppm: 1.41 (9H, *s*, *t*-Bu), 1.87 (6H, *s*, $C(CH_3)_2$), 7.35-7.89 (3H, *m*, C^6, C^7 and C^8-H), 8.31 (1H, *d*, J=8.1 Hz, C^5-H), 9.85 (1H, *br s*, OH). *Anal.* Calcd for $C_{16}H_{20}N_2O_4$: C, 63.14; H, 6.62; N, 9.20. Found: C, 63.12; H,

6.60; N, 9.07.

1-(3-*t*-Butoxycarbonyl-4(3*H*)-quinazolinon-2-yl)cyclohexanol (**5**): White needles (recryst. from hexane-ethyl acetate). mp 199-203 ^{o}C. Eluate=hexane-ethyl acetate (2:1-1:1). ^{1}H-NMR ($CDCl_3$) ppm: 1.20-2.53 (10H, *m*, cyclohexyl-H), 1.41 (9H, *s*, OBu-*t*), 7.32-7.58 (1H, *m*, C^6-H), 7.58-7.80 (2H, *m*, C^7 and C^8-H), 8.27 (1H, *d*, J=7.5 Hz, C^5-H), 9.53 (1H, *br s*, OH). *Anal.* Calcd for $C_{19}H_{24}N_2O_4$: C, 66.26; H, 7.02; N, 8.13. Found: C, 66.25; H, 6.94; N, 8.10.

Deprotection of *N*-*t*-Butoxycarbonyl group (General procedure of Table 2): TFA was added to a solution of the substrate (**2**-**5**) in dichloromethane (12 mL) at rt and stirred until the reaction was complete (checked by TLC). The reaction mixture was neutralized by 1 *N* sodium hydrooxide, extracted with dichloromethane. Organic layer was dried over sodium sulfate and purified with silica gel chromatography to give the product.

2,2-Dimethyl-1-(4(3*H*)-quinazolinon-2-yl)-1-propanol (**6**): Colorless prisms (recryst. from hexane-ethyl acetate). mp 169-172 ^{o}C. ^{1}H-NMR ($CDCl_3$) ppm: 1.06 (9H, *s*, *t*-Bu), 3.74 (1H, *d*, J=5.5 Hz, OH), 4.37 (1H, *d*, J=5.5 Hz, CH), 7.30-7.88 (3H, *m*, C^6, C^7 and C^8-H), 8.26 (1H, *dd*, J=7.6 Hz, 0.9 Hz, C^5-H), 10.59 (1H, *br s*, NH). *Anal.* Calcd for $C_{13}H_{16}N_2O_2$: C, 67.21; H, 6.94; N, 12.06. Found: C, 67.21; H, 6.80; N, 12.01.

Phenyl(4(3*H*)-quinazolinon-2-yl)methanol (**7**): Pale yellow needles (recryst. from hexane-ethyl acetate). mp 213-215 ^{o}C. ^{1}H-NMR (DMSO-d_6) ppm: 5.46 (1H, *br s*, CH), 6.26 (1H, *br s*, OH), 7.06-7.85 (8H, *m*, C^6, C^7, C^8 and phenyl-H), 7.97 (1H, *d*, J=8.1 Hz, C^5-H), 12.30 (1H, *brs*, NH). *Anal.* Calcd for $C_{15}H_{12}N_2O_2$: C, 71.40; H, 4.79; N, 11.10. Found: C, 71.60; H, 4.80; N, 10.92.

2-(4(3*H*)-Quinazolinon-2-yl)-2-propanol (**8**): Colorless prisms (recryst. from hexane-ethyl acetate). mp 159-161 ^{o}C. ^{1}H-NMR ($CDCl_3$) ppm: 1.72 (6H, *s*, $C(CH_3)_2$), 3.93 (1H, *s*, OH), 7.32-7.60 (1H, *m*, C^6-H), 7.60-7.93 (2H, *m*, C^7 and C^8-H), 8.30 (1H, *d*, J=8.1 Hz, C^5-H), 11.08 (1H, *br s*, NH). *Anal.* Calcd for $C_{11}H_{12}N_2O_2$: C, 64.70; H, 5.92; N, 13.72. Found: C, 64.75; H, 5.91; N, 13.52.

1-(4(3*H*)-Quinazolinon-2-yl)cyclohexanol (**9**): Colorless prisms (recryst. from hexane-ethyl acetate). mp 202 ^{o}C. ^{1}H-NMR ($CDCl_3$) ppm: 1.10-2.40 (10H, *m*, cyclohexyl-H), 3.73 (1H, *s*, OH), 7.30-7.60 (1H, *m*, C^6-H), 7.60-7.90 (2H, *m*, C^7 and C^8-H), 8.26 (1H, *d*, J=8.1 Hz, C^5-H), 10.86 (1H, *br s*, NH). *Anal.* Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.84; H, 6.60; N, 11.62.

REFERENCES

1. P. Schmidt and J. Druey, *Helv. Chim. Acta*, 1956, **39**, 986; R. K. Robins, *J. Am. Chem. Soc.*, 1956, **78**, 784; G. B. Elion and G. H. Hitchings, *J. Am. Chem. Soc.*, 1956, **78**, 3508.
2. S. Gabriel and R. Stelzner, *Ber. Dtsch.Chem. Ges.*, 1896, **29**, 1300.
3. O. Sugimoto, M. Mori, and K. Tanji, *Tetrahedron Lett.*, 1999, **40**, 7477; O. Sugimoto, M. Mori, K. Moriya, and K. Tanji, *Helv. Chim. Acta*, 2001, **84**, 1112.
4. K. Smith, G. A. El-Hiti, M. F. Abdel-Megeed, and M. A. Abdo, *J. Org. Chem.*, 1996, **61**, 647.
5. W. L. F. Armarego, *Adv. Heterocycl. Chem.*, 1963, **1**, 253.