Communications

The Thiazole Route to 2-Formyl-1β-Methylcarbapenem

Jin Soo Lee†, Do Kyu Pyun†, Won Koo Lee†, and Cheol Hae Lee*

Korea Research Institute of Chemical Technology, P.O. Box 107, Yusung, Taejon 305-600, Korea
†Department of Chemistry, Sogang University, Seoul 121-742, Korea
Received June 11, 1998

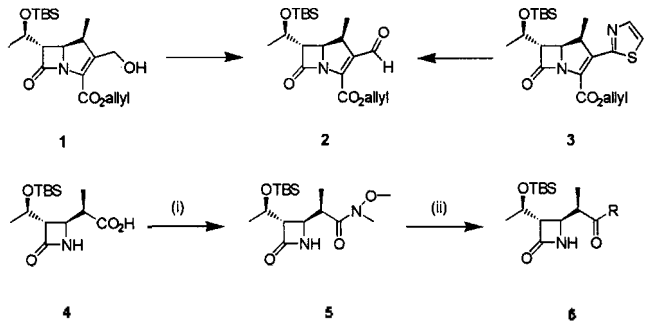
2-Formyl-1β-methylcarbapenem **2** can be used as a versatile intermediate to prepare potent carbapenem antibiotics. Only one method, reported by Shionogi group,[1] described the oxidation of the 2-hydroxymethylcarbapenem **1**[2] which was unstable to keep at room temperature. Shionogi method was lengthy and required such expensive reagents as trimethylsilyltriflate and titanium tetrachloride. In the course of our research to develop oral carbapenem antibiotics, we have found a new method that is focused on the use of thiazole as a synthetic equivalent to the formyl group.[3]

The commercially available 1β-methylazetidinone **4**[4] was condensed with *N,O*-dimethylhydroxyamine by the mixed anhydride coupling[5] to give the Weinnreb amide **5** in 87% yield. Reaction of **5** with 2-thiazolylmagnesium bromide prepared from 2-bromothiazole and ethylmagnesium bromide went smoothly to afford 2-thiazolylketone **6a**.

As can be seen in Table 1, weinnreb amide **5** reacted smoothly in most cases with aryl, alkyl, alkenyl and allyl organometallic reagents to give various ketones in high isolated yields (Scheme 1).

Subsequent application of the literature procedure[6] for cyclization of **6a** to the carbapenem led to the successful synthesis of 2-thiazolyl-1β-methylcarbapenem **3** (Scheme 2). The stablilized ylide **7** was prepared in 66% yield *via* a three-step sequence: 1) Condensation of **6a** with allyl glyoxylate, 2) Chlorination of the corresponding hemiaminal, 3) Ylide formation. Cyclization of ylide **7** in refluxing toluene provided carbapenem **3** in 91% yield[7].

The last step for the synthesis of 2-formyl-1β-methylcarbapenem **2** was the aldehyde release from the thiazole of **3**. The cleavage of the thiazole ring by the standard one-pot protocol[8] involving *N*-methylation, reduction and hydrolysis

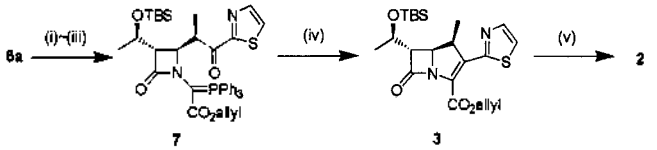


Scheme 1. Reagents and reaction conditions: (i) *i*-BuOCOCl, *N*-methylmorpholine, *N,O*-dimethylhydroxyamine hydrochloride (**5**: 87%); (ii) nucleophile, (**6**: 75~93%).

Table 1. Synthesis of β-Methylazetidinone Ketones **6a-6f** *via* the Weinnreb amide **5**

Enry	Nucleophile	Method[a]	Solvent	Temp (°C)	Time (hr)	Product (-R)	Yield[b] (%)
1		A	Et_2O	25	2	 (6a)	83
2		A	THF	- 40	2	 (6b)	86
3		A	THF	- 40	2	 (6c)	93
4		A	THF	25	4	 (6d)	83
5		B	Et_2O	25	6	 (6e)	75
6		B	Et_2O	20	1	 (6f)	87

[a] Method A: A solution of **5** was added to the Nucleophile in solvent under Ar at the indicated reaction temperature. Method B : reverse addition. [b] Yield refers to pure products isolated by flash column chromatography on silica gel 60 (230-400 mesh).



Scheme 2. Reagents and reaction conditions: (i) $HCOCO_2$allyl, toluene, reflux; (ii) $SOCl_2$, 2,6-lutidine, THF; (iii) PPh_3, 2,6-lutidine, dioxane, NaBr (**7**: 66%); (iv) toluene, reflux (**3**: 91%); (v) 1. $CF_3SO_3CH_3$, CH_3CN, rt, 10 min, 2. $NaBH_4$, MeOH, 0 °C to rt, 30 min, 3. $HgCl_2$, CH_3CN-H_2O (10 : 1), rt, 2 h. (**2** : 58%).

gave the desired 2-formyl-1β-methylcarbapenem **2** in 58% yield.[7]

In conclusion, a new synthesis of 2-formyl-1β-methylcarbapenem **2** was successfully achieved in 23-26% overall yield for the five steps from the commercially available 1β-methylazetidinone **4**. Weinnreb amide **5**[7] reacted with 2-thiazolylmagnesium bromide to afford ketone **6a**[7] in 83% yield. Conversion of thiazole ring into aldehyde **2** was accomplished by the one-pot process.

The application of this method to the preparation of C2-functionalized-1β-methylcarbapenems has been investigated in our laboratory.

Acknowledgment. We would like to thank Professor Jahyo Kang (Sogang University) for helpful guide and discussions. The authors are grateful to Ministry of Science and Technology (MOST) of Korea for financial support.

References

1. Imuta, M.; Itani, H.; Nishi, K.; Ona, H.; Kimura, Y. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2199.
2. Freshly prepared 2-hydroxymethylcarbapenem **1** should be used for MnO_2 oxidation due to its unstability at room temperature.
3. Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 835.
4. This compound is available from Takasago Chemical Co., Ltd, Japan.
5. Angelastro, M. R.; Peet, N. P.; Bey, P. *J. Org. Chem.* **1989**, *54*, 3913.
6. Schmitt, S. M.; Saltzmann, T. N.; Shih, D. H.; Christensen, B. G. *J. Antibiot.* **1988**, *41*, 780.
7. Physical data: **2**; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.05 (6H, s), 0.85 (9H, s), 1.20 (6H, m), 3.35 (1H, dd, J=5.1, 3.4 Hz), 3.46 (1H, m), 4.24 (1H, m), 4.29 (1H, dd, J=10.3, 3.4 Hz), 4.79 (2H, m), 5.28 (1H, dd, J=10.3, 1.4 Hz), 5.43 (1H, dd, J=17.2, 1.4 Hz), 5.88-5.97 (1H, m), 10.32 (1H, s). ^{13}C NMR (50 MHz, $CDCl_3$) δ −5.1, −4.2, 16.2, 17.9, 22.1, 25.6, 37.9, 56.3, 60.3, 65.3, 66.7, 119.2, 130.5, 141.9, 159.1, 172.1, 188.8.
3; mp 58-61 °C IR ($CDCl_3$) cm^{-1} 3403, 2957, 1779, 1465, 1386, 1275. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.09 (3H, s), 0.10 (3H, s), 0.89 (9H, s), 1.29 (3H, d, J=6.2 Hz), 1.30 (3H, d, J=7.3 Hz), 3.22 (1H, dd, J=6.2, 2.8 Hz), 4.07 (1H, m), 4.27 (2H, m), 4.82 (2H, m), 5.29 (1H, dd, J=10.5, 1.4 Hz), 5.46 (1H, dd, J=17.2, 1.4 Hz), 5.93-6.02 (1H, m), 7.51 (1H, d, J=3.0 Hz), 7.94 (1H, d, J=3.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.9, −4.1, 17.0, 18.0, 22.5, 25.7, 43.5, 55.8, 59.9, 66.2, 118.7, 122.9, 127.3, 131.2, 142.1, 142.8, 158.4, 161.1, 172.8. HR EI-MS m/z calcd for $C_{22}H_{32}N_2O_4SSi$ 448.1857, Found 448.1877.
5; mp 93-95 °C IR ($CDCl_3$) cm^{-1} 3157, 2968, 1760, 1650, 1469, 1386, 1253. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.04 (3H, s), 0.06 (3H, s), 0.83 (9H, s), 1.14 (3H, d, J= 6.3 Hz), 1.16 (3H, d, J=7.0 Hz), 2.97 (1H, dd, J=4.7, 2.2 Hz), 3.12 (1H, m), 3.19 (3H, s), 3.70 (3H, s), 3.84 (1H, dd, J=4.7, 2.2 Hz), 4.18 (1H, m), 6.06 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.1, −4.4, 12.4, 17.8, 22.2, 25.6, 31.9, 37.7, 52.0, 61.3, 65.1, 168.4, 175.1. FAB-MS (m/z) 345 (M^+)
6a; mp 103-106 °C IR ($CDCl_3$) cm^{-1}; 3098, 2971, 1761, 1673, 1477, 1387, 1258. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04 (3H, s), 0.05 (3H, s), 0.86 (9H, s), 1.11 (3H, d, J= 6.3 Hz), 1.32 (3H, d, J=7.0 Hz), 3.07 (1H, dd, J=4.0, 2.2 Hz), 4.01 (1H, dd, J=5.1, 2.2 Hz), 4.16 (2H, m), 6.04 (1H, br), 7.74 (1H, d, J=3.0 Hz), 8.03 (1H, d, J=3.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.1, −4.4, 12.6, 17.8, 22.3, 25.7, 43.7, 51.6, 61.6, 64.9, 127.1, 144.8, 166.4, 168.2, 195.5. HR EI-MS m/z calcd for $C_{17}H_{28}N_2O_3SSi$ 368.1589, Found 368.1570.
8. Dondoni, A.; Perrone, D.; Merino, P. *J. Org. Chem.* **1995**, *60*, 8074.

Formation of *o*-/*p*-Quinomethanes and *p*-Quinodimethanes from the Photoaddition of Diphenylacetylene to *o*-Quinones†

Ae Rhan Kim, Yoon Jung Mah, and Sung Sik Kim*

Department of Chemistry, Chonbuk National University, Chonju 561-756, Korea

Quinones are an important class of compounds as quinone dye-stuffs in industry or dehydrating agents in organic synthesis in addition to a vital role in biological systems. Due to their various spectroscopic properties, the photochemistry of quinones has been a subject of interest in many areas.[1,2] Our interest in diverse reactivity of excited quinones has promoted us to investigate the type of the photoadducts of quinones.[3-5] Bryce-Smith *et al.* have reported that tetrachloro-1,2-benzoquinone **1a** reacts photochemically with diphenylacetylene (DPA) **2** to give dioxenes.[6] Photoreaction of **1a** and **2** in acetone or acetonitrile at >400 nm gave 1 : 2 adduct as 1,4-dioxene. We found that, when irradiated with 300 nm UV light, *o*-quinones add to **2** to give two isomeric *o*-quinomethanes, *i.e.*, **4** and **5**, **8** and **9**, and **12** and **13**, *via* spiro-oxetene intermediates, like **3**.[7]

Recently, we found an interesting fact that irradiation (300 nm) of tetrahalo-1,2-benzoquinones **1** and DPA **2** in dichloromethane gave new type of *p*-quinomethanes **6**, as well as two isomeric *o*-quinomethanes, **4** and **5**, as shown in Scheme 1. Preparative photochemical reactions were conducted in a photoreactor composed of a water-cooled system and a Pyrex reaction vessel with 300 nm UV lamps (Rayonet Photochemical Reactor, Model RPR-208), after purging with nitrogen gas (purity; 99.9%) for 30 min. The photoproducts were isolated by flash column chromatography (silica gel, 230-400 mesh, Merck Co.) using *n*-hexane and ethyl acetate as the eluents (from 97 : 3 to 9 : 1, v/v).

Irradiation of a dichloromethane solution (100 mL) of tetrachloro-1,2-benzoquinone **1a** (246 mg, 1.0 mmol) and DPA **2** (178 mg, 1.0 mmol) with 300 nm UV light for 24 h afforded not only two isomeric *o*-quinomethanes, **4a** (26%) and **5a** (28%), *via* unstable spiro-oxetene **3a**, but also a novel *p*-quinomethane **6a** (17%).[8] The absorption peaks for

† This paper is dedicated to Professor Sang Chul Shim on the occasion of his 60th birthday.