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Facile Preparation of the Synthon of 7-Ethyl-8-oxabicyclo[4.3.0]nonane-2,9-dione

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The useful synthon of 7-ethyl-8-oxabicyclo[4.3.0]2,9-dioxononane was readily synthesized by a facile method. Starting from ethyl-1-bromo-2-oxocyclohexane- carboxylate, the 7-ethyl-8-oxabicyclo[4.3.0]nonane-2,9-dione was obtained by subsequent reactions of elimination, addition and reduction in total 49.4% yield. It showed no significant cytotoxicity to Bel7402 in the preliminary cytotoxicity assay study.

Key Words: 7-Ethyl-8-oxabicyclo[4.3.0]nonane-2,9-dione, Michael addition, Bromination, Keto-ester.

INTRODUCTION

In connection with our synthetic approaches to the concentricolide[1] which was originated from fungal secondary metabolites and showed anti HIV-1 activity,7-ethyl-8-oxabicyclo[4.3.0]nonane-2,9-dione (**1**) was once needed as an important intermediate. Such tetrahydroisobenzofuran-1,7(3*H*,7a*H*)-diones were also useful for synthesis of natural products[2]. However, up to now this type of compounds was all prepared by multiple reactions[3] in modest yields, especially preparation methods of the tetrahydroisobenzofuran-1,7(3*H*,7a*H*)-diones with alkyls at 8 position of the furan lactones have not been reported. Herein, a facile and efficient method to synthesize 7-ethyl-8-oxabicyclo[4.3.0]nonane-2,9-dione under mild conditions is reported.

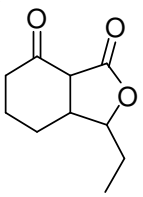


Fig. 1. Structure of 7-ethyl-8-oxabicyclo[4.3.0]nonane-2,9-dione (**1**)

EXPERIMENTAL

NMR spectra were recorded on Bruker AM-400 and Bruker DRX-500 spectrometers. FAB-MS was recorded with a VG Autospec-3000 spectrometer and HR-ESI-MS was recorded with an API QSTAR Pulsar 1 spectrometer. Silica gel (200-300 mesh, Qingdao Marine Chemical Inc., China) was used for column chromatography. Fractions were monitored by TLC and spots were visualized by heating silica gel plates sprayed with 10 % H_2SO_4 in ethanol. Combustion analysis was performed by Analysis Center of Henan Normal University. All commercial agents were produced by Sigma-Aldrich.

Preparation of ethy-6-bromo-1,4-dioxaspiro[4,5]-decane-6-carboxylate (3): A flask fitted with a Dean-Stark trap was charged with a solution of ethyl-1-bromo-2-oxocyclo-hexanecarboxylate **2** (2.988 g, 12.00 mmol), ethylene glycol (7.20 mL, 128.62 mmol) and *p*-toluenesulfonic acid (0.380 g, 2.00 mmol) in benzene (250 mL). The reaction mixture was heated at reflux overnight, cooled to room temperature, washed with 10 % aqueous $NaHCO_3$, water and saturated NaCl, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (petroleum ether-EtOAc, 15:1) to afford **3** (2.995 g, 85 % yield) as colourless oil: TLC (petroleum ether-Et_2O, 4:1) R_f 0.36. ^1H NMR (500 MHz, $CDCl_3$): δ 4.04-3.99 (m, 2H), 3.88-3.75 (m, 4H), 1.84-1.70 (m, 3H), 1.57-1.47 (m, 3H), 1.38-1.33 (m, 1H), 1.70-1.24 (m, 1H), 1.16-1.12 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.02 (C), 108.28 (C), 64.96 (CH_2), 64.54 (CH_2), 61.55 (C), 59.97 (CH_2), 34.31 (CH_2), 26.94 (CH_2), 23.05 (CH_2), 22.63 (CH_2), 13.91 (CH_3). FAB^+ m/z (%): 293 (100), 295 (95). Anal. calcd. (%) for $C_{11}H_{17}O_4Br$: C, 45.07; H, 5.85. Found (%): C, 45.03; H, 5.91.

Preparation of ethyl-1,4-dioxaspiro[4,5]dec-6-ene-6-carboxylate (4): Lithium carbonate (0.444 g, 6.00 mmol) and

lithium chloride (0.0427 g, 1.00 mmol) were added to ethyl 6-bromo-1,4-dioxaspiro[4,5]decane-6-carboxylate **3** (2.932 g, 10.00 mmol) in dry dimethylformamide (100 mL). The mixture was heated at 90-95 ºC and kept for 5 h, cooled to room temperature, diluted with 200 mL of ice water and extracted twice with 200 mL portions of Et_2O. The combined organic phase was washed twice with 50 mL portions of water, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography (petroleum ether-EtOAc, 15:1) to afford **4** (1.953 g, 92 % yield) as colourless oil: TLC (petroleum ether-EtOAc, 4:1) R_f 0.49. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (dt, 1H, *J* = 4.0 Hz, 1.7 Hz), 4.25-4.16 (m, 4H), 4.05-3.99 (m, 2H), 2.23 (m, 2H), 1.79 (m, 4H), 1.30 (t, 3H, *J* = 8.5 Hz). ^{13}C NMR (100MHz, $CDCl_3$): δ 165.17 (C), 145.32 (CH), 131.62 (C), 105.69 (C), 65.42 (CH_2), 65.39 (CH_2), 60.02 (CH_2), 34.92 (CH_2), 25.59 (CH_2), 19.74 (CH_2), 14.00 (CH_3). FAB$^+$ m/z (%): 213 (100), 111 (35), 97 (40), 83 (55), 41 (48). Anal. calcd. (%) for $C_{11}H_{16}O_4$; C, 62.25; H, 7.60; found (%): C, 62.23; H, 7.66.

Synthesis of ethyl-7-propionyl-1,4-dioxaspiro[4,5]-decane-6-carboxylate (5): Benzoyl peroxide (290.8 mg, 1.20 mmol) was added to a mixture of **4** (318.4 mg, 1.50 mmol) and propionaldehyde (304.9 mg, 5.25 mmol) in benzene (10 mL). The reaction was vigorously stirred under reflux with N_2 protection. More benzoyl peroxide (290.8 mg, 1.20 mmol) was added twice at 3 h intervals. The crude reaction mixture was concentrated and subjected to silica gel column chromatography (petroleum ether-EtOAc, 6:1) to give **5** (328.4 mg, 81 %) as a slight yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.15 (m, 2H), 4.01 (m, 1H), 3.94-3.82 (m, 3H), 3.22 (m, 1H), 3.00 (m, 1H), 2.63 (m, 1H), 2.51 (m, 1H), 2.01 (m, 1H), 1.80 (m, 2H), 1.68 (m, 1H), 1.48 (m, 1H), 1.26 (m, 3H), 1.15 (m, 1H), 1.04 (m, 3H). ^{13}C NMR (100MHz, $CDCl_3$): δ 212.25 (C), 171.19 (C), 108.84 (C), 64.65 (CH_2), 64.49 (CH_2), 60.36 (CH_2), 51.44 (CH), 50.22 (CH), 35.28 (CH_2), 34.17 (CH_2), 27.59 (CH_2), 22.55 (CH_2), 13.86 (CH_3), 7.33 (CH_3). FAB$^+$ m/z (%): 271 (5), 225 (19), 181 (12), 97 (34), 81 (46), 69 (72), 55 (100). HRESI m/z: Found (%) 271.155075, calcd. (%) for: $C_{14}H_{23}O_5$, $[M + H]^+$, 271.154549. Anal. calcd. (%) for $C_{14}H_{22}O_5$; C, 62.20; H, 8.20; found (%): C, 62.19; H, 8.22.

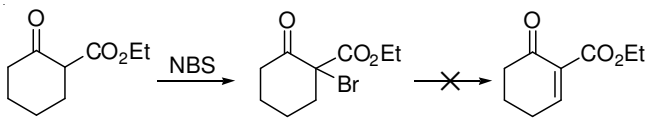
Preparation of 1'-ethylhexahydrospiro[[1,3]- dioxo-dioxane-2,4'-inden]-3'-(3a'H)-one (6): To a solution of **5** (335.4 mg, 1.24 mmol) in EtOH (15 mL) was added $NaBH_4$ (141.4 mg, 3.72 mmol) in two portions at 0.5 h intervals with stirring. The mixture was kept under stirring for 4 h at room temperature. At the end of the reaction, the solvent was evaporated and the crude reaction mixture was washed with water, extracted with ether, dried over sodium sulfate. The organic phase was filtered and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography (petroleum ether-EtOAc, 15:1) to afford **6** (218.9 g, 78 % yield) as a white form: ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.32 (td, 1H, *J* = 8.8 Hz, 3.2 Hz), 4.10 (m, 1H), 4.02 (m, 1H), 3.93 (m, 2H), 2.86 (d, 1H, *J* = 8.2 Hz), 2.40 (m, 1H), 1.81-1.42 (m, 8H), 1.06 (t, 3H, *J* = 7.4Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.20 (C), 107.73 (C), 83.16 (CH), 65.61 (CH_2), 64.72 (CH_2), 49.50 (CH), 41.00 (CH), 34.06 (CH_2), 26.46 (CH_2), 22.49 (CH_2), 19.07 (CH_2), 10.28 (CH_3). Anal. calcd. (%) for $C_{12}H_{18}O_4$; C, 63.70; H, 8.02; found (%): C, 63.65; H, 8.03.

Preparation of 7-ethyl-8-oxabicyclo[4.3.0]-2,9-dioxononane (1): To a solution of **6** (226.5 mg, 1 mmol) in 5 mL CH_2Cl_2 was added 72 % $HClO_4$ 0.5 mL dropwise at -5 to 0 ºC. The mixture was stirred at the same temperature for 4 h then poured cautiously into 75 mL of cold saturated Na_2CO_3. After dilution of the mixture with 50 mL of saturated NaCl, the product was isolated by extraction with Et_2O. The organic phase was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford **1** (218.4 mg, 100 % yield) as a very slight red solid: ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.18 (m, 1H), 3.50 (d, 1H, *J* = 8.1 Hz), 2.70 (m, 1H), 2.48-2.22 (m, 2H), 2.04-2.01 (m, 2H), 1.77 (m, 2H), 1.64 (m, 2H), 1.01 (t, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.49 (C), 171.14 (C), 85.64 (CH), 53.65 (CH), 42.97 (CH), 40.13 (CH_2), 26.55 (CH_2), 22.90 (CH_2), 22.05 (CH_2), 9.81 (CH_3). Anal. calcd. (%) for $C_{10}H_{14}O_3$; C, 65.91; H, 7.74; found (%): C, 65.90; H, 7.77.

Cytotoxicity assay of 7-ethyl-8-oxabicyclo[4.3.0]-nonane-2,9-dione: The compound was dissolved in DMSO as 100 mg/mL stock solutions before use and stored at -20 ºC. Human liver cancer Bel7402 cells (the American Type Culture Collection, Rockville, MD) were cultured in MEM medium supplemented with 10 % fetal bovine serum. Bel7402 cells were maintained in a 37 ºC, 5 % CO_2 humidified incubator. For cytotoxicity assays, 5000 of HepG2 cells were plated in 100 µL per well into 96-well micro titer plates. Cells were allowed to adhere for 24 h. Each compound ranging from 0.1-100 µg/mL in 100 µL was added to cells in duplicate wells. After 24 h incubation, cell viability was determined by sulforhodamine B (SRB) assay.

RESULTS AND DISCUSSION

In this work, ethyl-1-bromo-2-oxocyclohexanecarboxylate (**2**) was once used as a starting material to obtain the 1,3-diketone compound ethyl-6-oxocyclohex-1-enecarboxylate for Michael addition and the compound **2** was readily prepared by bromination of the commercially available ethyl-2-oxocyclohexanecarboxylate with NBS. But as Brenner[4] had pointed, dehydrobromination of ethyl-1-bromo-2-oxocyclohexanecarboxylate could not give the ethyl 6-oxocyclohex-1-enecarboxylate, but complex compounds (**Scheme-I**). The successful preparation schemes of ethyl-6-oxocyclohex-1-enecarboxylate were two: the one that Kato's method by multiple reactions starting from ethyl acetoacetate (**Scheme-II**)[5] and the other that phenylselenylation of ethyl-2-oxocyclohexanecarboxylate and then oxidative deselenylation[6].



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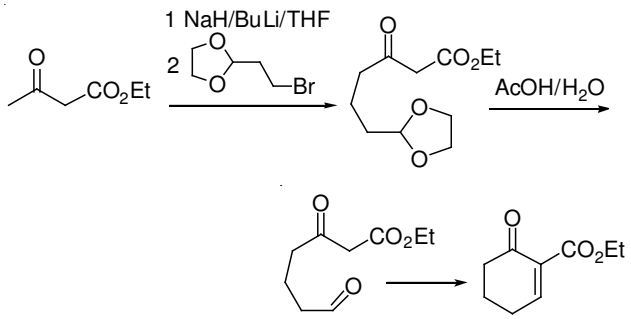
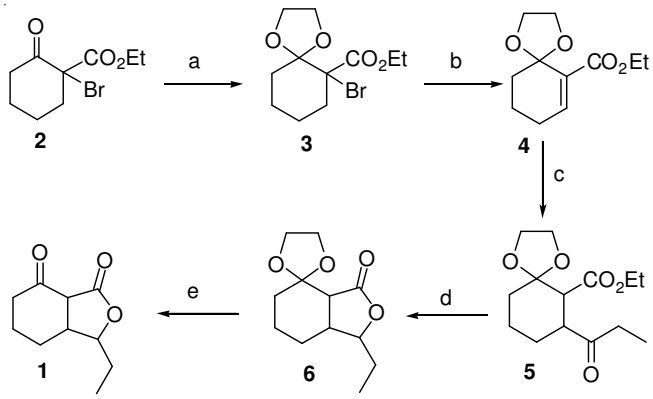
Scheme-I: Unsuccessful preparation of ethyl 6-oxocyclohex-1-enecarboxylate

Unfortunately, ethyl 6-oxocyclohex-1-enecarboxylate was not proved to be suitable for synthesis of the furan lactones because it was not stable and easily aromatization in our later experiments. In present plan, we protected the carbonyl group of **2** with ethylene glycol to give **3** and then obtained the



Scheme-II: Kato's method of preparation of ethyl 6-oxocyclohex-1-enecarboxylate

desired compound **4** successfully by dehydrobromination of **3**. Michael addition of **4** with propionaldehyde gave the racemate compound **5**. Reduction of **5** by $NaHB_4$ gave the lactone **6** in one step. Deprotection of **6** with $HClO_4$ afforded the 7-ethyl-8-oxabicyclo[4.3.0]2,9-dioxononane in quantitative yield (**Scheme-II**). It was noteworthy that there was no stereoselectivity by this method and all produced stereoisomers were collected as a racemate to reaction in the next step, we only focused on its use for construction carbon skeleton of 7-ethyl-8-oxabicyclo[4.3.0]2,9-dioxononane and the stereoselectivity of all compounds was not discussed here.



Scheme-III: Preparation of 7-ethyl-8-oxabicyclo[4.3.0]2,9-dioxononane (**1**)

Reagents and conditions: (a) *p*-$TsOH{\cdot}H_2O$, $HOCH_2CH_2OH$, benzene, reflux, (85 %). (b) Li_2CO_3/LiCl, DMF, 90-95 ºC (92 %). (c) $(PhCO_2)_2$, propionaldehyde, benzene (81 %). (d) $NaBH_4$, EtOH, room temperature (78 %). (e) $HClO_4$, CH_2Cl_2 (100 %).

The compound **6** showed cytotoxicity to Bel7402 with IC_{50} value 52.3 µg/mL. Its cytotoxicity to Bel7402 was obviously not significant and that convinced us that a simple lactone ring was not sufficient to obtain bioactive isobenzofuranones.

Conclusion

A facile method for preparation of 7-ethyl-8-oxabicyclo[4.3.0]nonane-2,9-dione has been established starting from ethyl-1-bromo-2-oxocyclohexanecarboxylate and it can be utilized to synthesize various furan lactones and analogues with different alkyls when the corresponding aldehydes were used in Michael addition reactions.

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REFERENCES

1. L.Z. Fang and J.K. Liu, *Heterocycles*, **78**, 2107 (2009).
2. G. Hollauf and E. Urban, *Monatsh. Chem*., **126**, 1203 (1995).
3. D.J. Goldsmith, T.K. John and F.V. Middlesworth, *Synth. Commun*., **10**, 551 (1980).
4. J.E. Brenner, *J. Org. Chem*., **26**, 22 (1961).
5. M. Kato, V.P. Kamat and A. Yoshikoshi, *Synth. Commun*., **18**, 699 (1988).
6. E. Urban, G. KnÜhl and G. Helmchen, *Tetrahedron*, **52**, 971 (1996).