Communication

NBS-Promoted Rearrangement of 1,1-Diarylmethylenecyclopentane

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Received June 15, 2011; Accepted August 19, 2011; Published Online August 30, 2011

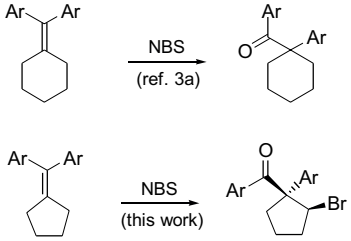
The 1-aroyl-1-aryl-2-bromocyclopentanes **3a**, **3b**, **3c** and **3d** (Ar = C_6H_5, 2-FC_6H_4, 3-FC_6H_4, 4-FC_6H_4) were prepared from *N*-bromosuccinimide (NBS)-promoted rearrangement of 1,1-diarylmethylenecyclopentane **2**. The possible mechanism was proposed. Two 1-phenyl-cyclopentane carbamides **5a** and **5b** with the anti-influenza effect were also accomplished from compound **3a**.

Keywords: 1,1-Diarylmethylenecyclopentane; *N*-Bromosuccinimide; Rearrangement.

INTRODUCTION

N-Bromosuccinimide (NBS) serves as an important and useful synthetic reagent in a variety of reactions.[1-2] NBS is a source of free-radical or positive bromine, used primarily in the bromination of organic substrates. A major use is in the bromination of allylic or benzylic positions (Wohl-Ziegler reaction) in the substrate. Other potential uses are *para*-bromination of phenol,[2a] Biginelli reaction,[2b] Hunsdiecker reaction,[2c] oxidative deprotection of ether,[2d] conversion of alcohols to bromides,[2e] *E*/*Z* isomerization,[2f] formation of heterocycles,[2g] and oxidation of reactive substrates.[2h] Recently, we have developed a facile NBS-mediated rearrangement reaction of 1,1-diarylmethylenecyclohexane under mild and base-free bromination condition.[3] This study showed that an efficient synthetic approach for preparing the skeleton of 1-aroyl-1-arylcyclohexane by NBS. In this article, NBS-mediated rearrangement reaction of 1,1-diarylmethylenecyclopentane was further investigated (Scheme I).

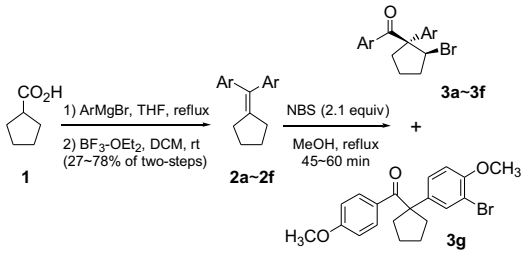
Scheme I NBS-mediated rearrangement reaction



RESULTS AND DISCUSSION

Cyclopentanecarboxylic acid (**1**) was chosen as the starting materials for the NBS-mediated rearrangement reaction, as shown in Table 1. Initially, skeleton **2** was provided by the Grignard addition of acid with 4.0 equivalents of arylmagnesium bromide (1.0 M in tetrahydrofuran, Ar = **a**, C_6H_5; **b**, 2-FC_6H_4; **c**, 3-FC_6H_4; **d**, 4-FC_6H_4; **e**, 4-$CH_3C_6H_4$; **f**, 4-$CH_3OC_6H_4$) at reflux for 10 h, followed by boron trifluoride etherate (BF_3-OEt_2)-mediated dehydration of the resulting tertiary alcohol in dichloromethane at rt for 1 h.[4] Compounds **2a**~**2f** were isolated in 27~78% total yields of

Table 1. Synthesis of 1-aroyl-1-aryl-2-bromocyclopentanes **3**[a]



Ar = **a**, C_6H_5; **b**, 2-FC_6H_4; **c**, 3-FC_6H_4; **d**, 4-FC_6H_4; **e**, 4-$CH_3C_6H_4$; **f**, 4-$CH_3OC_6H_4$

Entry	Ar group	**2** / Yield (%)	**3** / Yield (%)
1	C_6H_5	**2a** / 78	**3a** / 66
2	2-FC_6H_4	**2b** / 27	**3b** / ~ 10
3	3-FC_6H_4	**2c** / 55	**3c** / 31
4	4-FC_6H_4	**2d** / 68	**3d** / 52
5	4-$CH_3C_6H_4$	**2e** / 41	**3e** / trace
6	4-$CH_3OC_6H_4$	**2f** / 50	**3f** / trace; **3g** / 45%

[a] The products are > 95% pure as judged by ^{1}H-NMR analysis.

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two steps. The structure of compound **2d** was determined using single-crystal X-ray analysis (Fig. 1).[5]

Furthermore, treatment of skeleton **2** with NBS (2.1 equiv) in methanol at reflux for 45~60 min was converted into skeleton **3**. The compounds **3a**, **3b**, **3c** and **3d** were isolated in 66%, ~10%, 31% and 52% yield, respectively.[6] The structure of compound **3a** was determined using single-crystal X-ray analysis (Fig. 2).[5] The total procedure was monitored by TLC until the skeleton **2** was consumed.

To investigate the optimal reaction condition, compound **2a** was chosen as the starting material in the synthesis of skeleton **3**. We found that the reasonable reaction time and reaction temperature are the important issues. When the reaction time increased to 90 min at reflux, the yield of compound **3a** was obtained in only 37% yield. In the other way, when the reaction was carried out at rt for 10 h, we found that the provided products included 22% of starting material **2a** and 27% of compound **3a**. But, treatment of compound **2a** with an excess amount of NBS (3.1 equiv.) in methanol, major complex product was obtained. Attempts to examine the rearrangement reaction of compound **2a** with *N*-chlorosuccinimide (NCS) failed, perhaps due to an insufficient reactivity.

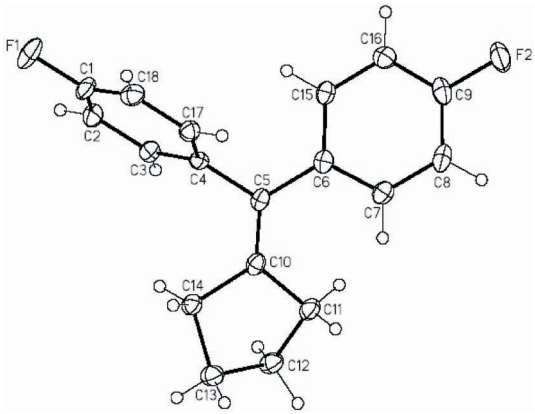


Fig. 1. X-Ray structure of compound **2d**.

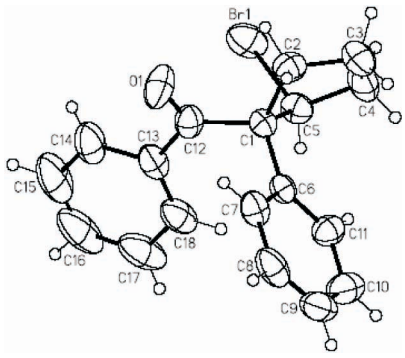
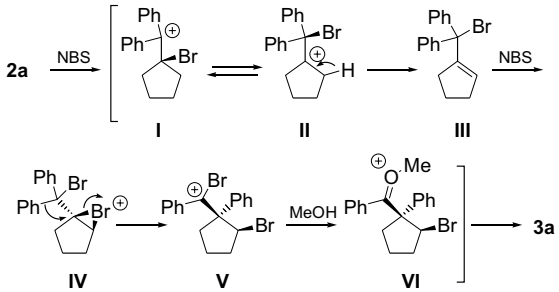


Fig. 2. X-Ray structure of compound **3a**.

The possible explanation for the interesting transformation from compound **2a** to **3a** could be that NBS-mediated rearrangement was induced by involvement of bromonium ion on the *exo*-olefinic position of cyclopentane skeleton (Scheme II). The initial event may be considered to be the formation of bromonium ion via the equilibrium between intermediate **I** and **II**. Hydrogen abstraction of intermediate **II** provided intermediate **III**. Then, treatment of intermediate **III** with the second equivalent of NBS gave intermediate **IV** with another bromonium ion. Next, intermediate **V** was formed by an 1,2-aryl group sigmatropic shift of intermediate **IV** from the back-side face. By the introduction of methanol on the tertiary carbocation, intermediate **VI** might be generated. Further, compound **3a** was yielded via the methanolysis of intermediate **VI**.

Scheme II The possible mechanism of compound **2a**

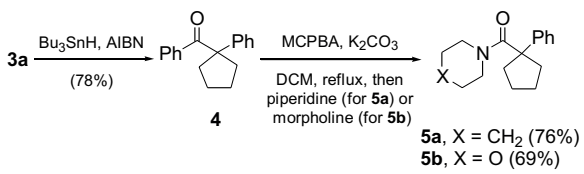


Treatment of compound **2b** (Ar = 2-FC_6H_4, for entry 2) with NBS was generated compound **3b** in low yield (~ 10%) under the above-mentioned condition. After changing the reaction temperature, time and equivalents of NBS, product **3b** could be only provided in a trace amount. Probably, the rearranged procedure was affected by the fluoro atom on the 2-position of phenyl group. In the preparation of compounds **3c** (Ar = 3-FC_6H_4, for entry 3) and **3d** (Ar = 4-FC_6H_4, for entry 4), the above reaction condition could provide 31% and 52% yields. For NBS-mediated rearrangement reaction of compound **2e** with 4-methylphenyl group (Ar = 4-$CH_3C_6H_4$, for entry 5), the complex product mixture was observed. This result showed that NBS might promote the *in situ* benzylic bromination to occur at the position of 4-methyl group. When compound **2f** was reacted with NBS (Ar = 4-$CH_3OC_6H_4$, for entry 6), a trace amount of compound **3f** was isolated. Especially, compound **3g** was afforded in 45% yield. In comparison with the elec-

tron-withdrawing fluoro group and electron-donating methoxy group, it was believed that 4-methoxyphenyl group should provide a stabilizing factor for the formation of intermediate **I** with a tertiary benzylic carbocation. Further, compound **3g** could be formed via addition of benzylic carbocation with methanol, oxygen lone-pair promoted 1,2-aryl shift and *ortho*-bromination by the second equivalent of NBS. The exhibited results were similar to the reported phenomena.[3] Based on the results, we found that the similar products (1-aroyl-1-arylcyclopentane and 1-aroyl-1-arylcyclohexane) could be obtained from the NBS-mediated rearrangement reaction of 1,1-diarylmethylenecyclopentane and 1,1-diarylmethylenecyclohexane with the electron-donating methoxy functional group. Although the synthetic application is limited, this presented rearrangement method is novel.

While poring over recent literature,[7] we found that 1-phenylcycloalkane carbamide, containing the similar structure to 1-arylcyclopentyl group, exhibited high activity against influenza viruses. With the idea in mind, the simple synthesis of 1-phenyl-cyclopentane carbamides **5a** and **5b** was further achieved from compound **3a** via a two-step procedure. One step is the azobisisobutyronitrile (AIBN)-mediated radical debromonination of compound **3a** with tri-*n*-butyltin hydride. The other step is the regioselective Baeyer-Villiger reaction of the corresponding compound **4** with *m*-chloroperoxybenzoic acid (MCPBA) under the basic reflux condition and followed by the nucleophilic addition of the resulting phenyl ester with piperidine (for compound **5a**) and morpholine (for compound **5b**) in reflux (Scheme III). Two compounds, **5a** and **5b**, with the biological activities were isolated in 76% and 69% yield, respectively, in one-pot reactions.[8]

Scheme III Synthesis of compounds **4a** and **4b**



In summary, we have successfully presented a convenient synthetic methodology for producing the 1-aroyl-1-aryl-2-bromocyclopentanes from the NBS-mediated reaction of 1,1-diarylmethylenecyclopentane. Synthesis of two 1-phenyl-cyclopentane carbamides with the anti-influenza effect is also accomplished.

ACKNOWLEDGEMENTS

The authors would like to thank the National Science Council of the Republic of China for its financial support (NSC 99-2113-M-037-006-MY3). The project is also supported by a grant from the Kaohsiung Medical Research Foundation (KMU-Q100004).

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5. CCDC 829110 (**2d**) and CCDC 784043 (**3a**) contain the supplementary crystallographic data for this paper. This data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: 44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).
6. A representative synthetic transformation of skeleton **3** from **2** is as follows: NBS (374 mg, 2.1 mmol) was added to a solution of skeleton **2** (1.0 mmol) in MeOH (10 mL) at rt. The reaction mixture was stirred at reflux for 45~50 min. Saturated $NaHCO_{3(aq)}$ (2 mL) was added to the reaction mixture and the solvent was concentrated. The residue was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product. Purification on silica gel (hexanes/EtOAc = 10/1~6/1) afforded skeleton **3**. For compound **3a**: M.p. = 121-122 °C; HRMS (ESI, M^++1) calcd for $C_{18}H_{18}BrO$ 329.0541, found 329.0542; ^{1}H NMR (400 MHz): δ 7.61-7.58 (m, 2H), 7.46-7.43 (m, 2H), 7.40-7.34 (m, 3H), 7.30-7.24 (m, 3H), 5.10 (d, *J* = 5.2 Hz, 1H), 2.86 (ddd, *J* = 9.2, 10.0,

13.6 Hz, 1H), 2.56-2.33 (m, 3H), 2.13-2.02 (m, 1H), 1.77-1.63 (m, 1H); ^{13}C NMR (100 MHz): δ 198.96, 139.67, 137.76, 131.72, 129.18 (2x), 128.77 (2x), 128.03 (2x), 127.56, 126.39 (2x), 69.12, 58.60, 35.63, 34.05, 20.46. Single-crystal X-ray diagram: crystal of compound **3a** was grown by slow diffusion of EtOAc into a solution of compound **3a** in DCM to yield colorless prism. The compound crystallizes in the monoclinic crystal system, space group P 1 21/n 1, a = 9.5922(11) Å, b = 15.0043(17) Å, c = 11.0273(12) Å, V = 1256.6(3) Å^3, Z = 4, d_{calcd} = 1.432 g/cm^3, F(000) = 672, 2θ range 2.35~26.39°, R indices (all data) R1 = 0.0811, wR2 = 0.1313. For compound **3b**: Oil; HRMS (ESI, M^++1) calcd for $C_{18}H_{16}BrF_2O$ 365.0353, found 365.0358; ^{1}H NMR (400 MHz): δ 7.36-7.28 (m, 2H), 7.22 (s, 1H), 7.19 (s, 1H), 7.13-7.10 (m, 2H), 7.00-6.99 (m, 2H), 5.06 (dt, J = 1.6, 5.6 Hz, 1H), 2.91-2.83 (m, 1H), 2.60-2.50 (m, 1H), 2.45-2.34 (m, 2H), 2.17-2.09 (m, 1H), 1.86-1.77 (m, 1H); ^{13}C NMR (100 MHz): δ 197.33, 163.96 (d, J = 240.6 Hz), 161.50 (d, J = 241.3 Hz), 143.55 (d, J = 5.7 Hz), 140.33 (d, J = 5.3 Hz), 131.99, 130.67, 128.69, 126.73, 120.22, 118.69, 114.35, 112.13, 60.23, 58.32, 36.02, 33.91, 20.28. For compound **3c**: Oil; HRMS (ESI, M^++1) calcd for $C_{18}H_{16}BrF_2O$ 365.0353, found 365.0355; ^{1}H NMR (400 MHz): δ 7.36-6.99 (m, 8H), 5.02 (d, J = 5.2 Hz, 1H), 2.84 (ddd, J = 8.8, 10.0, 13.6 Hz, 1H), 2.57-2.47 (m, 1H), 2.42-2.31 (m, 2H), 2.13-2.04 (m, 1H), 1.76-1.63 (m, 1H); ^{13}C NMR (100 MHz): δ 197.10, 163.20 (d, J = 246.3 Hz), 162.26 (d, J = 245.5 Hz), 142.12 (d, J = 6.0 Hz), 139.40 (d, J = 6.1 Hz), 130.89 (d, J = 7.6 Hz), 129.80 (d, J = 8.3 Hz), 124.38 (d, J = 3.1 Hz), 122.05 (d, J = 3.1 Hz), 119.05 (d, J = 21.9 Hz), 115.70 (d, J = 22.7 Hz), 114.89 (d, J = 21.2 Hz), 113.68 (d, J = 22.7 Hz), 63.98, 57.41, 35.71, 34.40, 20.40. For compound **3d**: Oil; HRMS (ESI, M^++1) calcd for $C_{18}H_{16}BrF_2O$ 365.0353, found 365.0355; ^{1}H NMR (400 MHz): δ 7.64-7.59 (m, 2H), 7.40-7.35 (m, 2H), 7.09-7.03 (m, 2H), 6.98-6.92 (m, 2H), 5.10 (dt, J = 1.2, 5.2 Hz, 1H), 2.85 (ddd, J = 8.8, 10.0, 13.6 Hz, 1H), 2.55-2.45 (m, 1H), 2.42-2.30 (m, 2H), 2.13-2.02 (m, 1H), 1.75-1.64 (m, 1H); ^{13}C NMR (100 MHz): δ 197.22, 164.59 (d, J = 272.1 Hz), 162.09 (d, J = 266.8 Hz), 135.44 (d, J = 3.8 Hz), 133.66 (d, J = 3.0 Hz), 131.46, 131.37, 128.11, 128.04, 116.36, 116.15, 115.38, 115.16, 68.44, 57.88, 35.58, 34.41, 20.44.

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8. For compound **5a**: M.p. = 57-58 °C; HRMS (ESI, M^++1) calcd for $C_{17}H_{24}NO$ 258.1858, found 258.1860; ^{1}H NMR (400 MHz): δ 7.31-7.27 (m, 2H), 7.22-7.16 (m, 3H), 3.56 (br s, 2H), 2.99 (br s, 2H), 2.45-2.39 (m, 2H), 2.04-1.95 (m, 2H), 1.78-1.66 (m, 6H), 151-1.45 (m, 2H), 0.99 (br s, 2H); ^{13}C NMR (100 MHz): δ 174.35, 145.95, 128.54 (2x), 125.94, 125.11 (2x), 58.55, 47.23, 43.86, 38.43 (2x), 25.23 (3x), 24.45 (2x). For compound **5b**: M.p. = 71-72 °C; HRMS (ESI, M^++1) calcd for $C_{16}H_{22}NO_2$ 260.1651, found 260.1652; ^{1}H NMR (400 MHz): δ 7.33-7.29 (m, 2H), 7.22-7.18 (m, 3H), 3.60 (br s, 4H), 3.10 (br s, 4H), 2.45-2.38 (m 2H), 2.04-1.95 (m, 2H), 1.77-1.69 (m, 4H); ^{13}C NMR (100 MHz): δ 174.75, 145.46, 128.77 (2x), 126.31, 125.03 (2x), 66.69, 65.86, 58.33, 46.94, 43.27, 38.33 (2x), 25.28 (2x).