HETEROCYCLES, Vol. 68, No. 11, 2006, pp. 2253 - 2257. © The Japan Institute of Heterocyclic Chemistry
Received, 28th August, 2006, Accepted, 2nd October, 2006, Published online, 3rd October, 2006. COM-06-10871

MICROWAVE-ASSISTED CYCLOADDITION REACTION OF AZIDES TO *N*-SUBSTITUTED 2-AZABICYCLO[2.2.1]HEPT-5-EN-3-ONES

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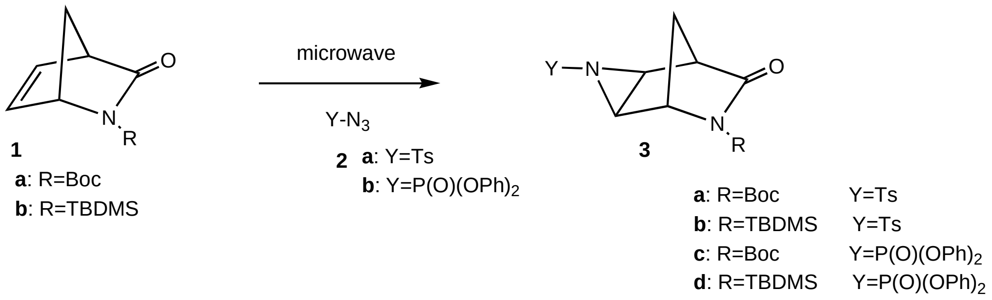
Abstract – The reaction of *N*-substituted 2-azabicyclo[2.2.1]hept-5-en-3-ones (ABH) (**1**) with azides (**2**,**4**) could be effected under microwave conditions, producing aziridine-fused ABH (**3**) and triazolines (**5**,**6**) in good yields.

Due to its attractive chemical diversity which is dependent on the increased ground state energy resulting from the great ring-strain in bicyclo[2.2.1]heptene system containing the amide group and the double bond, our interest was drawn to the synthetic exploration of 2-azabicyclo[2.2.1]hept-5-en-3-one (ABH) (**1**; R=H) as an important class of synthetic building block.[1] In connection with our project to prepare novel carbocyclic nucleosides,[2] we have previously disclosed the stereoselective addition of azides to **1a**.[3] In contrast to the known facile reaction of norbornene with benzoyl azide,[4] the attempted addition reaction of azides to **1a** under standard conditions was sluggish.[5] Eventually, the high-pressure was found to promote the 1,3-dipolar cycloaddition reaction to give triazolines, but it required a longer reaction time and caution in treating under high-pressure conditions. We found that the addition reaction time could be significantly reduced when the reaction was performed under microwave



Scheme 1

conditions, and herein present our preliminary results.

Despite the recent remarkable progress in microwave-assisted protocols in synthetic organic chemistry,[6] there have been few reports on microwave-assisted addition reaction of azides to double bond.[7]

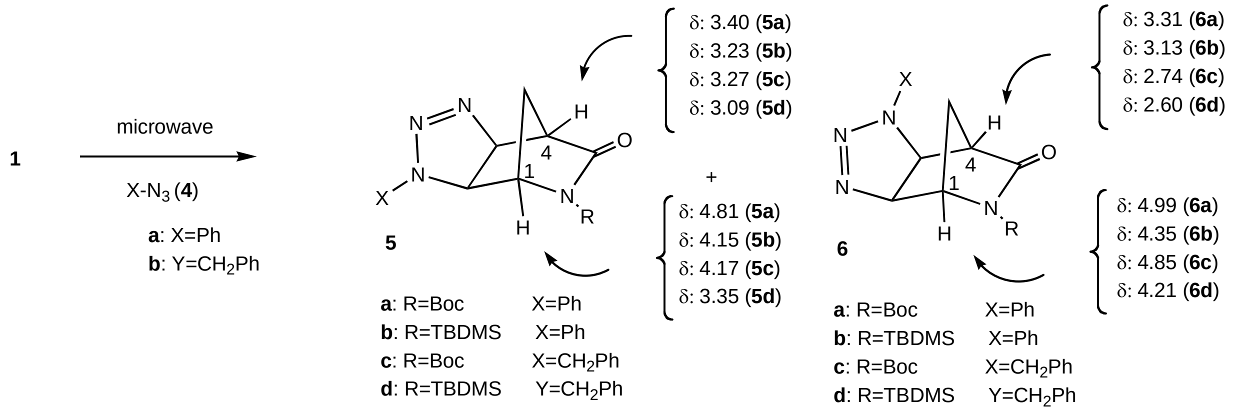
Initially, a mixture of *N*-Boc ABH (**1a**) and electron-poor **2a** (2 equiv) were irradiated in a microwave reactor at 100 to 140°C for 30 min with or without solvent,[8] resulting in the formation of aziridine-fused ABH (**3a**) through nitrene-addition[9] in low yields, along with substantial amounts of unchanged **1a** (Scheme 1 and Table 1). On the other hand, *N*-TBDMS ABH (**1b**) proved to be much more reactive toward **2a**. Microwave-irradiation of **1b** with **2a** at 140°C for 30 min allowed the isolation of **3b** in 63% yield. Similarly, **1b** reacted with **2b** at 140°C for 30 min to provide **3d** in 61% yield, as compared with the observed lower reactivity of **1a** toward **2b**.

Table 1 Microwave-assisted reaction of **1** with azides (**2**)

1	**2**	Conditions			Yield (%)[a] of **3**
1a	**2a**	140°C,	30 min,	in DMF	15 (**3a**)[2c]
1a	**2a**	100°C,	30 min,	in toluene	25 (**3a**)[2c]
1a	**2a**	120°C,	30 min,	without solvent	36 (**3a**)[2c]
1b	**2a**	140°C,	30 min,	in DMF	47 (**3b**)[10]
1b	**2a**	100°C,	30 min,	in toluene	58 (**3b**)[10]
1b	**2a**	140°C,	30 min,	without solvent	63 (**3b**)[10]
1a	**2b**	140°C,	60 min,	in DMF	10 (**3c**)[3]
1a	**2b**	140°C,	30 min,	without solvent	17 (**3c**)[3]
1b	**2b**	140°C,	60 min,	in DMF	33 (**3d**)[10]
1b	**2b**	140°C,	30 min,	without solvent	61 (**3d**)[10]

[a] Yields based on **1**

The reaction of **1** could also be performed with azides (**4**). This reaction proceeded to completion within 10 min, yielding a pair of regioisomeric triazolines (**5** and **6**) in good yields by way of 1,3-dipolar



Scheme 2

cycloaddition reaction (Scheme 2 and Table 2). After the reaction was complete, **5** and **6** were separated by SiO_2 column chromatography. The structures of **5** and **6** were assigned based on a comparison of chemical shifts of the H-1 and H-4 protons in ^{1}H-NMR spectrum, as reported previously.[3] The reactivity of **1a** toward **4** compares favorably with that of **1b**, and the reaction was best undertaken without solvent under microwave-conditions at 100℃ for 10 min.

Table 2 Microwave-assisted reaction of **1** with azides (**4**)

1	**4**	Conditions	Yield (%)[a] of **5**	Yield (%)[a] of **6**
1a	**4a**	140℃, 10 min, in DMF	22 (**5a**)[3]	39 (**6a**)[3]
1a	**4a**	100℃, 10 min, without solvent	23 (**5a**)[3]	49 (**6a**)[3]
1b	**4a**	140℃, 10 min, in DMF	21 (**5b**)[10]	45 (**6b**)[10]
1b	**4a**	100℃, 10 min, without solvent	24 (**5b**)[10]	55 (**6b**)[10]
1a	**4b**	140℃, 30 min, in DMF	23 (**5c**)[10]	36 (**6c**)[10]
1a	**4b**	100℃, 10 min, without solvent	28 (**5c**)[10]	53 (**6c**)[10]
1b	**4b**	140℃, 30 min, in DMF	27 (**5d**)[10]	36 (**6d**)[10]
1b	**4b**	100℃, 10 min, without solvent	31 (**5d**)[10]	52 (**6d**)[10]

[a] Yields based on **1**

In summary, we have disclosed an alternative protocol for the reaction of ABH (**1**) with azides (**2**, **4**) using microwave-irradiation, providing aziridine-fused ABH (**3**) and triazolines (**5**, **6**), respectively.

ACKNOWLEDGEMENTS

This was supported in part by “Academic Frontier” Project for Private University: matching fund subsidy from Ministry of Education, Culture, Sports, Science and Technology, 2002-2006, in part by a Grant-in Aid for High Technology Research Program from Ministry of Education, Culture, Sports, Science and Technology of Japan, and in part by a Grant-in Aid for Scientific Research (No. 18590011) from the Ministry of Education, Culture, Sports, Science and Technology of Japan. The authors thank Kuraray Co., Ltd. for providing the ABH.

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8. Microwave irradiation was carried out using Green-Motif I (IMCR-25003) microwave reactor (IDX Corporation). To a glass tube were added **1b** (1 mmol) and **2a** (2 mmol), and the vessel was placed into the cavity of microwave reactor. Microwave irradiation at 300 W was performed, the temperature being ramped from rt to 140°C. The mixture was let stand for 30 min. After cooling, the mixture was separated by medium pressure chromatography (SiO_2) with hexane-AcOEt.
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10. **3b**: ^{1}H-NMR ($CDCl_3$) δ: 0.21 (s, 3H), 0.32 (s, 3H), 0.89 (s, 9H), 1.52 (d, 1H, *J*=9.7 Hz), 1.86 (d, 1H, *J*=9.7 Hz), 2.45 (s, 3H), 2.84 (s, 1H), 3.28 (d, 1H, *J*=6.3 Hz), 3.43 (d, 1H, *J*=6.3 Hz), 3.94 (s, 1H), 7.35 (d, 2H, *J*=8.6 Hz), 7.80 (d, 2H, *J*=8.6 Hz). ^{13}C-NMR ($CDCl_3$) δ: -5.3, -4.9, 18.9, 21.7, 26.3, 33.0, 40.0, 44.1, 47.2, 58.4, 127.9, 129.9, 134.8, 145.0, 181.9. **3d**: ^{1}H-NMR ($CDCl_3$) δ: 0.19 (s, 3H), 0.28 (s, 3H), 0.91 (s, 9H), 1.54 (d, 1H, *J*=9.7 Hz), 1.86 (d, 1H, *J*=9.7 Hz), 2.82 (s, 1H), 3.25 (s, 1H), 3.28 (s, 1H), 3.86 (s, 1H), 7.18-7.21 (m, 6H), 7.32-7.35 (m, 4H). ^{13}C-NMR ($CDCl_3$) δ: -5.2, -4.8, 18.9, 26.4, 32.6, 37.6, 42.1, 47.3, 58.7, 120.3, 120.4, 125.5, 129.9, 182.6. **5b**: ^{1}H-NMR ($CDCl_3$) δ: 0.33 (s, 3H), 0.36 (s, 3H), 0.95 (s, 9H), 1.39 (d, 1H, *J*=10.9 Hz), 1.94 (d, 1H, *J*=10.9 Hz), 3.23 (s, 1H), 4.15 (s, 1H), 4.20 (d, 1H, *J*=9.2 Hz), 5.20 (d, 1H, *J*=9.2 Hz), 7.08 (t, 1H, *J*=7.4 Hz), 7.23-7.28 (m, 2H), 7.36 -7.39 (m, 2H). ^{13}C-NMR ($CDCl_3$) δ: -5.2, -4.8, 19.1, 26.3, 35.7, 51.4, 61.4, 62.3, 82.5, 114.0, 123.0, 129.8, 139.7, 181.0. **5c**: ^{1}H-NMR ($CDCl_3$) δ: 1.36 (td, 1H, *J*=1.7, 11.5 Hz), 1.43 (s, 9H), 1.85 (td, 1H, *J*=1.7, 10.9 Hz), 3.27 (s, 1H), 3.73 (d, 1H, *J*=9.2 Hz), 4.17 (s, 1H), 4.81 (d, 1H, J=14.9 Hz), 4.91 (d, 1H, *J*=14.9 Hz), 5.02 (d, 1H, *J*=9.2 Hz), 7.30-7.40 (m, 5H). ^{13}C-NMR ($CDCl_3$) δ: 28.1, 31.8, 52.1, 53.5, 61.5, 62.2, 83.1, 83.6, 128.4, 128.5, 129.1, 135.9, 148.7, 172.0. **5d**: ^{1}H-NMR ($CDCl_3$) δ: -0.12 (s, 3H), 0.12 (s, 3H), 0.80 (s, 9H), 1.38 (d, 1H, *J*=10.3 Hz), 1.80 (d, 1H, *J*=10.3 Hz), 3.09 (s, 1H), 3.35 (s, 1H), 3.46 (d, 1H, *J*=9.7 Hz), 4.64 (d, 1H, *J*=14.3 Hz), 4.95 (d, 1H, *J*=14.3 Hz), 4.98 (d, 1H, *J*=9.7 Hz), 7.31-7.40 (m, 5H). ^{13}C-NMR ($CDCl_3$) δ: -5.4, -5.5,

18.8, 26.2, 35.9, 51.7, 53.8, 62.3, 64.5, 83.2, 128.5, 128.7, 129.1, 135.9, 181.5. **6b**: ^{1}H-NMR (CDCl$_3$) δ: 0.32 (s, 3H), 0.34 (s, 3H), 0.96 (s, 9), 1.39 (d, 1H, *J*=10.9 Hz), 1.92 (d, 1H, *J*=10.9 Hz), 3.13 (s, 1H), 4.35 (s, 1H), 4.38 (d, 1H, *J*=9.2 Hz), 5.06 (d, 1H, *J*=9.2 Hz), 7.06-77.09 (m, 1H), 7.35-7.39 (m, 4H). ^{13}C-NMR (CDCl$_3$) δ: -5.1, -5.08, 18.9, 26.4, 35.8, 51.1, 57.0, 62.6, 88.5, 114.3, 123.1, 129.7, 139.3, 180.8. **6c**: ^{1}H-NMR (CDCl$_3$) δ: 1.36 (d, 1H, *J*=10.9 Hz), 1.50 (s, 9H), 1.90 (d, 1H, *J*=10.9 Hz), 2.74 (s, 1H), 3.77 (d, 1H, *J*=9.2 Hz), 4.72 (d, 1H, *J*=14.9 Hz), 4.85 (s, 1H), 4.96 (d, 1H, *J*=14.9 Hz), 5.01 (d, 1H, *J*=9.2 Hz), 7.25-7.37 (m, 5H). ^{13}C-NMR (CDCl$_3$) δ: 28.1, 32.2, 52.1, 53.0, 58.8, 62.1, 83.9, 86.7, 128.3, 128.5, 129.1, 135.4, 148.6, 172.1. **6d**: ^{1}H-NMR (CDCl$_3$) δ: 0.23 (s, 3H), 0.25 (s, 3H), 0.90 (s, 9H), 1.38 (d, 1H, *J*=10.3 Hz), 1.86 (d, 1H, *J*=10.3 Hz), 2.60 (s, 1H), 3.74 (d, 1H, *J*=9.3 Hz), 4.21 (s, 1H), 4.70 (d, 1H, *J*=14.3 Hz), 4.83 (d, 1H, *J*=9.3 Hz), 4.95 (d, 1H, *J*=14.3 Hz), 7.27-7.37 (m, 5H). ^{13}C-NMR (CDCl$_3$) δ: -5.2, -5.3, 18.9, 26.3, 36.3, 51.6, 52.7, 58.5, 62.7, 88.8, 128.3, 129.0, 135.8, 181.3.