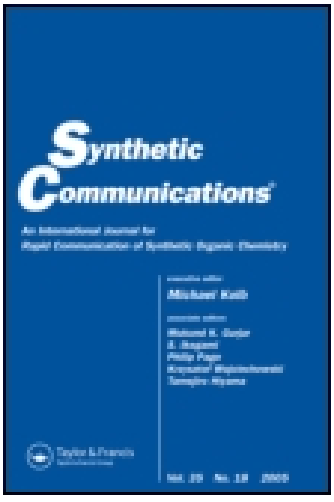


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis of Methyl 2-Methylazulene-3-carboxylate in the Presence of Molecular Sieves and Reaction with N-Bromosuccinimide

Dao-Lin Wang [a] , Jiao Xu [a] , Zheng Gu [a] , Shan Han [a] & Kimiaki Imafuku [b]
[a] College of Chemistry and Chemical Engineering, Liaoning Key Laboratory of Apple Chemistry , Bohai University , Jinzhou, China
[b] Faculty of Science, Department of Chemistry , Kumamoto University, Kurokami , Kumamoto, Japan
Published online: 22 Feb 2008.

To cite this article: Dao-Lin Wang , Jiao Xu , Zheng Gu , Shan Han & Kimiaki Imafuku (2008) Synthesis of Methyl 2-Methylazulene-3-carboxylate in the Presence of Molecular Sieves and Reaction with N-Bromosuccinimide, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 38:6, 991-996, DOI: 10.1080/00397910701818453

To link to this article: http://dx.doi.org/10.1080/00397910701818453

Synthetic Communications®, 38: 991–996, 2008

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910701818453

Synthesis of Methyl 2-Methylazulene-3-carboxylate in the Presence of Molecular Sieves and Reaction with *N*-Bromosuccinimide

Dao-Lin Wang,[1] Jiao Xu,[1] Zheng Gu,[1] Shan Han,[1] and Kimiaki Imafuku[2]

[1]College of Chemistry and Chemical Engineering, Liaoning Key Laboratory of Apple Chemistry, Bohai University, Jinzhou, China
[2]Faculty of Science, Department of Chemistry, Kumamoto University, Kurokami, Kumamoto, Japan

Abstract: The preparation of methyl 2-methylazulene-1-carboxylate (**1**) was carried out in the presence of molecular sieves to obtain a good yield. The product was subjected to bromination under different reaction conditions to obtain methyl 1-bromo-2-methylazulene-1-carboxylate (**2**) and methyl 1-bromo-2-(bromomethyl) azulene-1-carboxylate (**3**).

Keywords: bromination, 2-methylazulene, molecular sieves

INTRODUCTION

In many synthetic methods for azulenes, the reaction of 2*H*-cyclohepta[*b*]furan-2-one with enamines is an efficacious way of preparaing 1-substituted azulenes in good yield[1]; however, it was not as effective 2-substituted azulenes. The enamines can be conveniently prepared in high yield by the reaction of appropriate ketones and amines in the presence of molecular sieves.[2]

Address correspondence to Dao-Lin Wang, Faculty of Chemistry and Chemical Engineering, Bohai University, No. 19, Science and Technology Road, High-Tech Development District, Jinzhou 121001, China. E-mail: wangdaolin@sina.com

Table 1. Catalysis with molecular sieves in the preparation of 2-methylazulene

Entry	Molecular sieve	Time (h)	Product yield (%)
1	None	72	46
2	4 Å 0.6 g/mmol	24	75
3	4 Å 0.6 g/mmol	48	78
4	4 Å 0.3 g/mmol	48	73
5	4 Å 0.1 g/mmol	72	63
6	4 Å 1.2 g/mmol	18	76
7	3 Å 0.6 g/mmol	24	79
8	3 Å 0.3 g/mmol	48	76
9	3 Å 0.1 g/mmol	72	55

Molecular sieves simultaneously serve as dehydrating agent and catalyst that can be simply removed at the end of the reaction by filtration. Further, in some instances, the distillate has been dried effectively with molecular sieves.[3] Therefore, in the absence of molecular sieves, the reaction rate of ketone and amine is quite slow. To integrate enamine formation with azulene synthesis in onepot, the preparation of methyl 2-methylazulene-1-carboxylate (**1**) was carried out in the presence of molecular sieves. Good yields were obtained while reducing reaction time. The results are shown in Table 1.

2H-Cyclohepta[*b*]furan-2-one was treated with acetone and diethylamine, which are precursors to enamine, in the absence of molecular sieves under refluxing for 72 h. It afforded azulene (**1**) only in 46% yield[4] (entry 1). The yield of **1** increased when the reaction was carried out using molecular sieves sized 3 Å or 4 Å) (entries 2, 3, 4, and 8). The yield of **1** was optimized to 79% using 0.6 g/mmol of 3 Å molecular sieves (entry 7). The reactions using a small amount of molecular sieves resulted in low yields (entries 5 and 9). When 1.2 g/mmol of 4 Å molecular sieves were used, the reaction time reduced to 18 h, and azulene (**1**) was obtained in a good yield (entry 6).

Bromination of Methyl 2-Methylazulene-3-carboxylate with *N*-Bromosuccinimide (NBS)

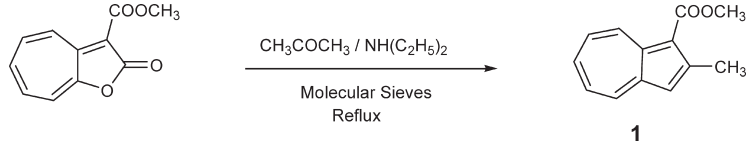
Electrophilic substitution of an aromatic ring using NBS has been observed,[5] although the results are highly variable in terms both of products and yields. In the absence of a metal chloride catalyst, bromination of benzene and toluene with NBS does not occur. However, in polynuclear aromatic hydrocarbons, the reaction was observed without catalyst.[6]

Halogenation of azulenes with *N*-halosuccinimide has been described by Anderson's group. The reaction of strongly nucleophilic compounds with NBS are generally considered to be ionic. It was presumed that the bromination of azulenes would involve substitution at the 1-position.[7]

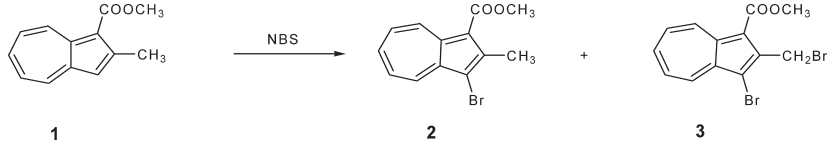
Table 2. Bromination of 2-methylazulene with NBS

				Yield (%)	
Entry	Molar ratio	Solvent	Reaction condition	**2**	**3**
1	1:1.2	C_6H_6	Rt, 1 h	97	—
2	1:2.2	C_6H_6	Reflux, 24 h	11	86
3	1:1	CCl_4	BOP, reflux, 1 h	86	7
4	1:2.2	CCl_4	BOP, reflux, 12 h	—	83

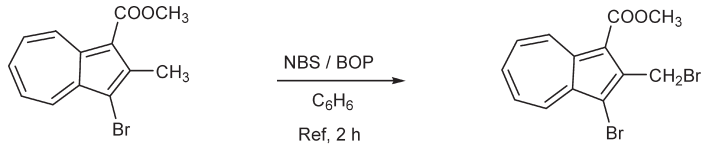
Reaction of 2-methylazulene (**1**) with NBS in a molar ratio of 1:1.2 at room temperature in benzene for 1 h gave 1-bromo-2-methylazulene (**2**) in excellent yield (Table 2, Entry 1). The reaction in a molar ratio of 1:2.2 under refluxing for 24 h in benzene afforded **2** in 11% yield and 1-bromo-2-(bromomethyl)azulene (**3**) in 86% yield, respectively (entry 2). On the other hand, reaction of an equimolar amount of 2-methylazulene (**1**) and NBS in refluxing carbon tetrachloride in the presence of the radical initiator, benzoyl peroxide (BOP), for 1 h gave 1-bromo-2-methylazulene (**2**) in excellent yields and a small amount of 1-bromo-2-(bromomethyl)azulene (**3**) (entry 3). The reaction of **1** in a similar condition in carbon tetrachloride only afforded methyl 1-bromo-2-(bromomethyl)-azulene-3-carboxylate (**3**) in 83% yield (entry 4). These results showed the bromination of 2-methylazulenes with NBS in the presence or absence of the radical initiator (BOP) at the 1-position of azulene priority afforded the corresponding 1-bromo-2-methylazulenes, whereas bromination at the 2-methyl group was not observed (Schemes 1 and 2).



Scheme 1.



Scheme 2.



2 3

Scheme 3.

In the radical bromination process, 1-bromo-2-methylazulene (**2**) was heated in refluxing benzene in the presence of benzoyl peroxide to provide 1-bromo-2-bromomethyl-azulenes (**3**) in 86% yield (Scheme 3).

In conclusion, we have found one new method for the preparation of methyl 2-methylazulene with improved yields in the presence of molecular sieves and have investigated the bromination using NBS. The bromination of 2-methylazulene derivatives with NBS in electrophilic aromatic substitution and under the radical conditions also were investigated.

EXPERIMENTAL

All melting points were determined with a Yanaco MP JP-3 apparatus and are uncorrected. The IR spectra were measured on a Jasco A-102 IR spectrophotometer. The NMR spectra were recorded with a Jeol JNM-EX 300 spectrometer (300 MHz for ^{1}H and 75.5 MHz for ^{13}C). Elemental analyses were performed at the Center for Instrumental Analysis, Beijing University.

Preparation of Methyl 2-Methylazulene-3-carboxylate (1) in the Presence of Molecular Sieves

Molecular sieves (3 Å, 3.0 g) were added to a mixed solution of methyl 2-oxo-2*H*-cyclohepta[*b*]furan-3-carboxylate (1.02 g, 5.0 mmol), acetone (20 ml), and diethylamine (7 ml). The reaction mixture was heated under refluxing for 24 h. The mixture were cooled to room temperature. The molecular sieves were filtered off and washed with solvent. The solvent was removed from the filtrate. The residue was poured into water (50 ml) and extracted with benzene (3 × 20 ml). The benzene layer was washed with water and with brine, then dried over sodium sulfate. After removal of the solvent, the residue was chromatographed on a silica-gel column with benzene as eluent to give **1** (790 mg, 79%) as purple prisms, mp 45–46°C (hexane) (lit.[6] 45–46°C).

Bromination of Methyl 2-Methylazulene-3-carboxylate (1) with NBS

N-bromosuccinimide (106 mg, 0.6 mmol) was added to a solution of methyl 2-methylazulene-3-carboxylate (**1**) (0.5 mmol) in benzene (20 ml). After stirring for 1 h at room temperature, cold water (20 ml) was added to the mixture. The combined organic layer and extracts were washed with water and dried over sodium sulfate. The evaporation residue was chromatographed on a silica-gel column with benzene as eluent. The blue fraction was collected and afforded 1-bromo-2-methylazulenes **2**.

Methyl 1-Bromo-2-methylazulene-3-carboxylate (2)

Blue crystals (benzene); mp 88–89°C IR (KBr): ν 1694 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.77 (3H, s, CH_3), 3.95 (3H, s, $COOCH_3$), 7.38 (1H, dd, $J = 9.9$, 9.6 Hz, 5- or 7-H), 7.42 (1H, dd, $J = 10.2$, 9.9 Hz, 7- or 5-H), 7.64 (1H, t, $J = 9.9$ Hz, 6-H), 8.31 (1H, d, $J = 9.9$ Hz, 8-H), 9.36 (1H, d, $J = 9.9$ Hz, 4-H); ^{13}C NMR ($CDCl_3$): 17.1 (CH_3), 51.0 ($COOCH_3$), 108.6 (═C<), 114.4 (═C<), 127.2 (═CH-), 128.1 (═CH-), 135.4 (═CH-), 136.6 (═CH-), 138.3 (═CH-), 140.6 (═C<), 151.1 (═C<), 165.7 ($COOCH_3$). Anal. calcd. for $C_{13}H_{11}BrO_2$: C, 55.94; H, 3.97%. Found: C, 56.19; H, 3.94%.

Bromination of Methyl 1-Bromo-2-methylazulene-3-carboxylate (2) with NBS

A solution of 1-bromo-2-methylazulenes (**2**) (0.5 mmol) in benzene (30 ml) containing finely powdered *N*-bromosuccinimide (1 mmol) and dibenzoyl peroxide (10 mg) was refluxed for 1 h. After the reaction mixture had been cooled, it was diluted with water and then extracted with dichloromethane. The extract was dried over sodium sulfate and evaporated in vacuo to leave a residue that was chromatographed on a silica-gel column with benzene as eluent to give 1-bromo-2-(bromomethyl)azulenes (**3**).

Methyl 1-Bromo-2-(bromomethyl)azulene-3-carboxylate (3)

Dark violet crystals (benzene); mp 99–101°C; IR (KBr): ν 1679 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.02 (3H, s, $COOCH_3$), 5.17 (2H, s, CH_2Br), 7.48 (1H, dd, $J = 11.1$, 9.9 Hz, 5 or 7-H), 7.52 (1H, dd, $J = 11.1$, 10.2 Hz, 7- or 5-H), 7.77 (1H, t, $J = 9.9$ Hz, 6-H), 8.46 (1H, d, $J = 9.0$ Hz, 8-H), 9.52 (1H, d, $J = 9.9$ Hz, 4-H); ^{13}C NMR ($CDCl_3$): 26.4 (CH_2Br), 51.5 ($COOCH_3$), 108.1 (═C<), 113.3 (═C<), 127.9 (═CH-), 128.8 (═CH-), 137.8 (═CH-), 138.8 (═C<), 139.0 (═CH-), 140.5 (═CH-), 140.7

(=C<), 146.9 (=C<), 164.9 ($COOCH_3$). Anal. Calcd. for $C_{13}H_{10}Br_2O_2$: C, 43.61; H, 2.81%. Found: C, 43.52; H, 2.81%.

ACKNOWLEDGMENT

The authors gratefully acknowledge the financial support of this work by the Ministry of Education of Liaoning Province of China (No. 2005021).

REFERENCES

1. Yasunami, M.; Miyoshi, S.; Kariko, N.; Takase, K. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 892.
2. Taguchi, K.; Westheimer, F. H. *J. Org. Chem.* **1971**, *36*, 1570.
3. Stork, G.; Brizzolara, A.; Landesman, H.; Szmuskovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1965**, *85*, 217.
4. Nozoe, T.; Takase, K.; Nakazawa, T.; Yukada, S. *Tetrahedron* **1971**, *27*, 3357.
5. (a) Djerassi, C. *Chem. Rev.* **1948**, *43*, 271; (b) Bovonsombat, P.; Mcnelis, E. *Synthesis* **1993**, 237.
6. (a) Schmid, H. *Helv. Chim. Acta.* **1946**, *29*, 1144; (b) Schmid, H.; Leutenegger, W. *Helv. Chim. Acta.* **1947**, *30*, 1965.
7. (a) Anderson, A. G.; Fritz, C. G.; Scotoni, R. *J. Am. Chem. Soc.* **1957**, *79*, 6511; (b) Scotoni, R.; Cowles, E. J.; Fritz, C. G. *J. Org. Chem.* **1957**, *22*, 1193; (c) Anderson, A. G.; Nelson, J. A.; Tazuma, J. *J. Am. Chem. Soc.* **1953**, *75*, 4980.