Heteroatom Chemistry
Volume 13, Number 4, 2002

A Tandem Reaction of 4-Bromoalkyl Aldehydes with Sodium Azide: Synthesis of 5,6,7,7a-Tetrahydro-pyrrolo[1,2-*d*]-[1.2.3.4]oxatriazole

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Received 20 July 2001; revised 2 September 2001

ABSTRACT: *5,6,7,7a-Tetrahydro-pyrrolo[1,2-d]-[1.2.3.4]oxatriazoles were synthesized through a nucleophilic substitution–cycloaddition tandem reaction of 4-bromoalkyl aldehydes with sodium azide.* Heteroatom Chem 13:307–309, 2002; Published online in Wiley Interscience (www.interscience.wiley.com). DOI 10.1002/hc.10035

INTRODUCTION

The development of tandem reaction processes has been a rapidly growing area of synthetic organic chemistry during recent years [1–4]. Tandem reactions, sometimes also called domino, sequential, cascade, consecutive, iterative, zipper, and one-pot reactions, link several transformations together in a single synthetic step. Typically, an initial reaction produces an intermediate that undergoes further transformations with strategically positioned reactive centers in the same molecule, with other compounds in the reaction mixture, or with additional reagents introduced after the initial transformation takes place. Over the last decade, tandem reactions have been widely used in syntheses of biologically active agents and natural products through various reaction sequences [3,4]. Functionalized pyrrolidines are compounds of considerable importance. They occur in a variety of natural products and pharmaceutically active compounds, either as isolated ring systems or embedded in more complex structures, which often possess widely ranging biological activity [5]. The development of the methodology for the preparation of highly functionalized pyrrolidines has attracted considerable interest recently [5–8]. Herein, I report a nucleophilic substitution–cycloaddition tandem reaction of 4-bromoalkyl aldehydes with sodium azide. It can be used to synthesize 5,6,7,7a-tetrahydro-pyrrolo[1,2-*d*][1.2.3.4]oxatriazoles.

RESULTS AND DISCUSSION

When a nucleophilic substitution reaction of 4-bromobutyraldehyde with sodium azide was carried out at room temperature, in addition to the desired product 4-azidobutyraldehyde (**2a**) [9], another colorless oil was also obtained. In its ^{1}H NMR, ^{13}C NMR, and IR spectra, no signal of a carbonyl group of an aldehyde was found. Its structure was assigned as a bicyclic compound, 5,6,7,7a-tetrahydro-pyrrolo[1,2-*d*][1.2.3.4]oxatriazole (**3a**). When the reaction temperature was reduced to 0°C, only **2a** was obtained. However, when the reaction temperature was increased to 50°C, compound **3a** was the sole product. And **2a** can convert to **3a** at 50°C. It is rationalized

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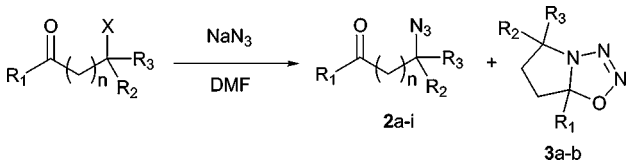
Contract grant sponsor: Tsinghua University.



SCHEME 1 Reaction of bromo/toluenesulfonyloxy aldehydes and ketones with sodium azide.

that a nucleophilic substitution–cycloaddition tandem reaction takes place between the 4-bromoalkyl aldehyde and sodium azide. 4-Bromobutyraldehyde and sodium azide first undergo a nucleophilic substitution to yield **2a**, which then undergoes an intramolecular [2 + 3] cycloaddition reaction to form **3a** (Scheme 1). According to my knowledge, this is the first synthesis of this kind of a bicyclic heterocyclic compound.

In order to extend this tandem reaction, a variety of bromo aldehydes have been tested (Table 1). It was found that both 4-toluenesulfonyloxybutyraldehyde [10] and 4-bromo-4-methylvaleraldehyde could undergo this tandem reaction to produce 5,6,7,7a-tetrahydro-pyrrolo[1,2-*d*][1.2.3.4]oxatriazoles **3a** and **3b**, respectively. However, 5-toluenesulfonyloxy-2-hexanone did not undergo this tandem reaction; it just gave 5-azido-2-hexanone. Even if it were refluxed in toluene, still no bicyclic product could be found. All of the other bromo aldehydes and ketones did not undergo this tandem reaction; they just gave nucleophilic substitution products, azido aldehydes, and ketones. The proposed mechanism for the formation of compounds **3** is presented in Scheme 2.

The proposed structures for unknown compounds **3a,b** are based on ^{1}H NMR, ^{13}C NMR, mass spectral, and elemental analyses.

In conclusion, a nucleophilic substitution–cycloaddition tandem reaction can take place between 4-bromo/toluenesulfonyloxy alkyl aldehydes and sodium azide. It can be used to synthesize 5,6,7,7a-tetrahydro-pyrrolo[1,2-*d*][1.2.3.4]oxatriazole derivatives.

EXPERIMENTAL

Melting points were obtained on a Yanaco melting point apparatus and are uncorrected. Elemental analyses were carried out on an Elementar Vario EL elemental analyzer. The ^{1}H NMR spectra were recorded on a Varian Inova 300 spectrometer with TMS as an internal standard in $CDCl_3$. The IR spectra were taken on a Brucker Vector 22 FT-IR spectrophotometer in KBr. Mass spectra were obtained on a VG ZAB-HS mass spectrometer. TLC separations were performed on silica gel G plates with petroleum ether (60–90°C)/ethyl acetate (10:1), and the plates were visualized with UV light.

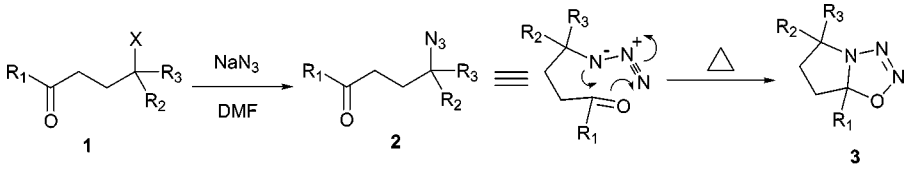
Reaction of Bromo/Toluenesulfonyloxy Aldehydes and Ketones with Sodium Azide

General Procedure. A mixture of bromo/toluenesulfonyloxy aldehyde or ketone 1 (2.5 mmol) and sodium azide (230 mg, 3.75 mmol) in DMF (5 ml) was stirred in an oil bath at 50°C overnight. The reaction mixture was diluted with ether/hexane (1:1, 25 ml), washed twice with water and twice with brine, dried over Na_2SO_4, and concentrated. Flash column chromatography on a silica gel column with a mixture of petroleum ether (60–90°C)/ethyl acetate (10:1) as the eluant gave colorless oils, azido aldehyde (or ketone) **2**, and/or 5,6,7,7a-tetrahydro-pyrrolo[1,2-*d*][1.2.3.4]oxatriazole **3**.

5,6,7,7a-Tetrahydro-pyrrolo[1,2-*d*][1.2.3.4]oxatriazole (**3a**): Colorless oil: ^{1}H NMR δ: 4.92 (t, J = 24.5 Hz, 1H, CH), 3.44 (t, J = 6.9 Hz, 2H, CH_2), 2.03 (m, 2H, CH_2), 1.84 (m, 2H, CH_2). ^{13}C NMR δ: 26.8, 32.9, 33.5, 100.4. MS/FAB m/z: 114 (MH^+). Anal.

TABLE 1 Reaction of Bromo/ Toluenesulfonyloxy Aldehydes and Ketones with Sodium Azide

Entry	*n*	*R_1*	*R_2*	*R_3*	*X*	*Reaction Temperature (°C)*	*Yield of **2** (%)*	*Yield of **3** (%)*
a	2	H	H	H	Br	0	84	–
						RT	36	52
						50	–	87
					TsO	50	–	85
b	2	H	Me	Me	Br	50	–	89
c	2	Me	H	H	Br	RT to 110	79	–
d	2	Me	H	Me	TsO	RT to 110	81	–
e	3	H	H	H	TsO	RT to 110	83	–
f	4	H	H	H	TsO	RT to 110	86	–
g	1	H	H	H	Br	RT to 110	72	–
h	0	H	H	H	Br	RT to 110	63	–
i	0	Me	H	H	Cl	RT to 110	70	–
j	0	Ph	H	H	Br	RT to 110	94	–



SCHEME 2 The proposed mechanism for the formation of compounds **3**.

Calcd. for $C_4H_7N_3O$ (113.06): C, 42.47; H, 6.24; N, 37.15. Found: C, 42.52; H, 6.30; N, 37.00.

5,6,7,7a-Tetrahydro-5,5-dimethyl-pyrrolo[1,2-*d*]-[1.2.3.4]oxatriazole (**3b**): Colorless oil. ^{1}H NMR δ: 4.92 (t, $J = 4.5$ Hz, 1H, CH), 2.03 (m, 2H, CH_2), 1.82 (m, 2H, CH_2), 1.09 (s, 6H, 2Me). ^{13}C NMR δ: 26.7, 30.2, 32.8, 33.4, 100.5. MS/FAB *m/z*: 142 (MH^+). Anal. Calcd. for $C_6H_{11}N_3O$ (141.17): C, 51.05; H, 7.85; N, 29.77. Found: C, 51.12; H, 7.79; N, 29.83.

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