



Electronic and steric effects on the intramolecular Schmidt reaction of alkyl azides with secondary benzyl alcohols



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ABSTRACT

The intramolecular Schmidt reaction of simple azido secondary benzyl alcohols has been realized for the first time. Investigation of the electronic and steric effects of the substrates on the product outcome was conducted. Unique intramolecular Schmidt rearrangements were observed with the formation of a cinnamaldehyde derivative and aryl aldehydes, respectively. Using this protocol, an efficient synthesis of dihydrobenzotriazine derivatives was achieved. Moreover, a practical approach to 2-aryl-1-pyrrolines was also accessed.

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1. Introduction

Two decades ago, the intramolecular Schmidt reaction of alkyl azides with ketones and tertiary carbocations was first reported by Aubé and Pearson independently.^{1,2} Since then, a considerable amount of research has been conducted on the optimizations of the reaction conditions,³ the applications in the synthesis of complex nitrogen-containing heterocycles,⁴ and expanding the substrate scope.⁵ Nevertheless, detailed studies are still warranted to address the steric and electronic effects of the substrates on these reactions.^{5b,j,m,p} For example, Molina et al. showed that the azido benzylic carbocations with the tether length of four-carbon between the azido group and the phenyl group could readily undergo intramolecular Schmidt reaction to give five-membered cyclic imines.^{5c} However, their attempts to make six-membered cyclic imines via Schmidt reaction of the azido benzylic carbocations with the tether length of five-carbon failed, without giving any explanation. On the other hand, although a variety of substrates have been explored in generating various electron-deficient systems for azide rearrangements,^{5h} surprisingly, there is so far no report on intramolecular Schmidt reactions based on simple azido secondary benzyl alcohols.^{5k,6}

This paper describes our study results on intramolecular Schmidt reaction of alkyl azides with secondary benzyl alcohols.

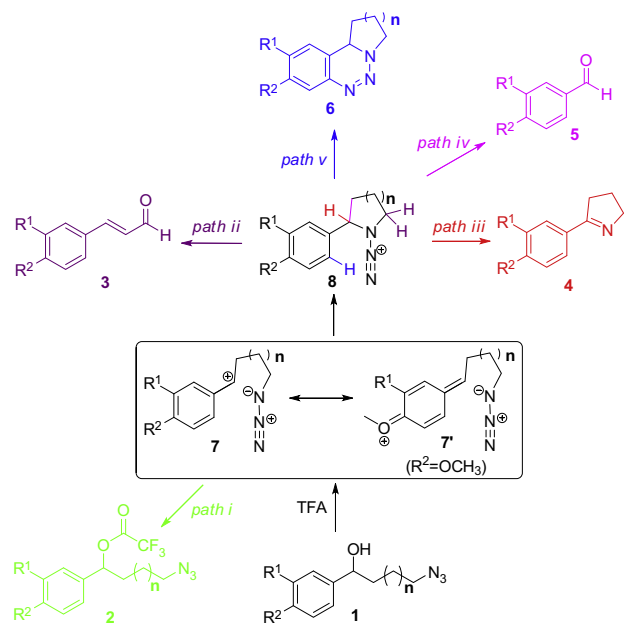
Particularly, we address the substituent effects of the phenyl ring and the tether lengths of the azido alkyl chains on the product outcome. Detailed mechanistic analysis is also presented herein.

2. Results and discussion

As shown in [Scheme 1](#), upon treatment of azido alcohols **1** with trifluoroacetic acid (TFA) at 0 °C, room temperature or 40 °C, products **2–6** were formed via paths i–v, respectively, depending on the length of azido alkyl chains and the electronic properties of the substituents at the phenyl ring. To test how the steric and electronic factors affected the product outcome, 19 substrates were examined ([Table 1](#)).

For azido alcohols **1** without substituents at the phenyl ring and with tether lengths of three-carbon (**1a**), five-carbon (**1l**), or six-carbon (**1p**), trifluoroacetic esters **2a**, **2l**, and **2p** were obtained as the major products (entries 1, 12, and 16) together with recovered starting materials, respectively. In contrast, for azido alcohol **1e** with tether length of four-carbon, five-membered cyclic imine **4e** was obtained as the major product (entry 5). This discrepancy might be due to that, given the instability of benzylic carbocations **7** without substitution at the phenyl ring, the steric difficulties in forming cyclic aminodiazonium ions **8** from **7** gave rise to the formation of trifluoroacetic esters **2a**, **2l**, and **2p**, respectively ([Scheme 1](#), path i). For example, the strain of the four-membered cyclic intermediate **8** derived from **1a** might be so strong that, before its formation, an intermolecular nucleophilic trapping of **7** by TFA

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Scheme 1. Reactions of azido alcohols **1** with TFA.

Table 1
Product outcome of the reactions of azido alcohols **1** with TFA^a

Entry	Azido alcohol	<i>n</i>	R ¹	R ²	Product	Yield ^b (%)
1	1a	0	H	H	2a	44
2	1b	0	H	CF ₃	— ^c	— ^c
3	1c	0	H	OCH ₃	— ^d	— ^d
4	1d	0	OCH ₃	OCH ₃	3d	31
5	1e	1	H	H	4e	56
6	1f	1	H	CF ₃	— ^c	— ^c
7	1g	1	H	CH ₃	4g	75
8	1h	1	H	Ph	4h	58
9	1i	1	H	OCH ₃	4i	74
10	1j	1	OCH ₃	OCH ₃	4j	65
11	1k	1	R ^e	OCH ₃	4k	63
12	1l	2	H	H	2l	37
13	1m	2	H	CF ₃	2m	58
14	1n	2	H	OCH ₃	5n	54
15	1o	2	OCH ₃	OCH ₃	5o	61
16	1p	3	H	H	2p	55
17	1q	3	H	CF ₃	— ^c	— ^c
18	1r	3	H	OCH ₃	5n	52
19	1s	3	OCH ₃	OCH ₃	6s/5o^f	73 ^f

^a Reaction temperature: rt for **1a**, **1e**, **1g**, **1h**, **1i**, and **1p**; 0 °C for **1c**, **1d**, **1i–k**, **1n**, **1o**, **1r**, **1s**; 40 °C for **1b**, **1f**, **1m**, and **1q**.

^b Isolated yields.

^c Starting materials recovered.

^d The reaction was complex and no products could be identified.

^e R=O(CH₂)₃OCH₃.

^f **6s/5o**=6.3:1.

occurred, leading to ester **2a** as the major product. In addition, the longer tether lengths in **7** derived from **1l** and **1p** might delay and disfavor the azido attack at the benzylic carbocations so that esters **2l** and **2p** became the dominant products, respectively. This well explains why Molina et al. failed to make six-membered cyclic imines via intramolecular Schmidt reaction.^{5c}

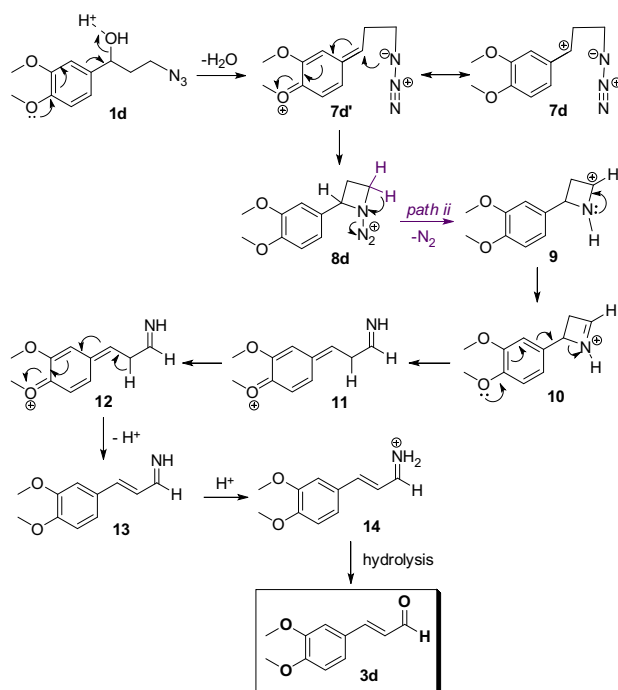
On the other hand, despite the instability of carbocation **7** derived from **1e**, the favored kinetics of five-membered ring formation readily gave rise to the corresponding aminodiazonium ion **8**, further leading to cyclic imine **4e** via benzylic hydride migration to the cyclic N atom with loss of nitrogen (Scheme 1, path iii).^{5c}

To test the effect of electron-withdrawing substituents of the phenyl ring on the product profile, azido alcohols **1b**, **1f**, **1m**, and **1q**

with different alkyl chain lengths were examined. Except for **1m** allowing for the formation of ester **2m** (entry 13), treatment of **1b**, **1f**, and **1q** with TFA at room temperature or at 40 °C all resulted in the recovery of the starting materials (entries 2, 6, 17), implying that electron-withdrawing groups disabled the generation of the corresponding benzylic carbocations **7**.

By contrast, azido alcohols **1** with electron-donating substituents at the phenyl ring were more susceptible to the Schmidt rearrangements (Scheme 1, paths ii, iii, iv), leading to different types of products **3–5**. This demonstrates that electron-donating groups promote the formation of stabilized benzylic carbocations **7** or *O*-methylated quinone methide cation **7'** (R²=OCH₃), thus allowing for the formation of aminodiazonium ions **8** as the precursors to Schmidt reactions. The product profile still depends on the alkyl chain lengths and the electronic properties of the substituents (entries 3, 4, 7–11, 14, 15, 18, 19). The possible mechanisms are discussed as below.

Scheme 2 elucidates the plausible mechanism for the formation of 3,4-dimethoxycinnamaldehyde **3d** from **1d** with tether length of three-carbon. We envisioned that, upon protonation of the benzylic hydroxyl group, the *p*-methoxy function in **1d** should play a key role as the secondary driving force through electron delocalization, leading to the quinone methide cation **7d'** as the first in situ generated species,⁷ instead of benzylic carbocation **7d**. In comparison with **7d**, **7d'** is so stable that the unfavored four-membered cyclic intermediate **8d** could be formed. The strain in **8d** favors a nonbenzylic hydride shift to the cyclic N atom with loss of nitrogen, leading to carbocation **9**. After a series of electron transfer and proton transfer steps, hydrolysis of aldimine ion **14** results in **3d**. On the other hand, an alternative mechanism involving decomposition of a cinnamyl azide under acidic conditions cannot be excluded,⁸ even though the generation of this cinnamyl azide in the presence of the *p*-methoxy function is questionable. To our knowledge, this is the first example for an intramolecular Schmidt reaction affording a cinnamaldehyde derivative as the major product.^{5k}



Scheme 2. Mechanism of formation of **3d** from **1d**.

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