Tetrahedron Letters 52 (2011) 6470-6472

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Thermally-induced skeletal rearrangement of (*Z*)-O-propargylic α , β -unsaturated aldoximes to multisubstituted pyridine oxides

Itaru Nakamura^{a,b,*}, Dong Zhang^b, Masahiro Terada^{a,b}

^a Research and Analytical Center for Giant Molecules, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan ^b Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan

ARTICLE INFO

ABSTRACT

Article history: Received 23 August 2011 Revised 20 September 2011 Accepted 22 September 2011 Available online 29 September 2011

Keywords: Pyridine Oxime Skeletal rearrangement Alkyne Electrocyclization

Multisubstituted pyridines are found in numerous natural and synthetic pharmaceutical agents.¹ Pyridine scaffolds are also of great interest in material science.² Therefore, there is still a need to develop efficient methodologies to synthesize pyridine derivatives, of which the substituents are introduced in a regioselective manner.³ We recently reported that the copper-catalyzed skeletal rearrangement of (*E*)-*O*-propargylic α , β -unsaturated aldoximes (*E*)-**1** afforded 2,3,4,(5)-multisubstituted pyridine oxides **2** in good to high yields (Eq. 1). ^{4–6} Herein, we report that the thermal

* Corresponding author.

E-mail address: itaru-n@m.tohoku.ac.jp (I. Nakamura).

cyclization of the corresponding *Z* isomers of *O*-propargylic oxime (*Z*)-**1** produced 2,3,6-trisubstituted pyridine oxides **3** that have a different substitution pattern from **2**, at an elevated temperature in the absence of a copper catalyst (Eq. 2).

(Z)-Propargylic oxime ethers derived from α_{β} -unsaturated aldehydes were converted to the correspond-

ing 2,3,6-trisubstituted pyridine oxides in moderate to acceptable yields with high regioselectivity. The

reaction proceeds via a tandem thermal [2,3] rearrangement, 4π electrocyclization, and ring expansion.

In our previous study, we reported that (*Z*)-1a was converted into four-membered cyclic nitrone **4a** in the presence of copper in fairly high yield (Table 1, entry 1).^{4a} In this reaction, a trace amount of 2,3,6-trisubstituted pyridine oxide 3a was detected by a thorough analysis of the crude mixture. The structure of 3a was determined by NMR, IR, and X-ray crystallographic analyses. The reaction of (*Z*)-**1a** proceeded even in the absence of the copper catalyst (entries 2, 4-14). Among the solvents tested, the use of polar DMF improved the mass balance, although a long reaction time was needed (entries 5–10). An apparent temperature effect was also observed; the yield of 3a was increased when the reaction temperature was elevated (entries 4, 5, 11-14). In particular, the reaction at 180 °C was completed within 15 min, affording 3a in a good isolated yield (entry 14). Although the copper complex exhibited catalytic activity for the formation of 4a in DMF at 100 °C (entry 3 vs entry 5) attempts to improve the chemical yield by optimizing the copper catalyst failed.

Thus, thermally-induced skeletal rearrangement at 180 °C was carried out using various substrates (*Z*)-**1**, as summarized in Table 2.⁷ The reaction of substrate **1b** having an electron-donating *p*-anisyl group at the β position of the oxime group (R⁴) afforded the desired product **3b** in a higher yield than that of **1c** that had an electron-withdrawing *p*-nitrophenyl group (entries 2 and 3). The reaction of **1e**, whose R³ is a hydrogen atom, afforded **3e** in a





© 2011 Elsevier Ltd. All rights reserved.

^{0040-4039/\$ -} see front matter @ 2011 Elsevier Ltd. All rights reserved. doi:10.1016/j.tetlet.2011.09.107

Table 1Optimization of the reaction conditions



Entry	Solvent	Copper catalyst ^a	Temp. (°C)	Time (h)	Yield 3a ^b (%)	Yield 4a ^b (%)
1	MeCN	+	100	7	7	84
2	MeCN	_	100	7	4	71
3	DMF	+	100	3	6	86
4	DMF	_	80	67	6	84 ^c
5	DMF	_	100	23	12	82
6	DMSO	_	100	23	9	48
7	DCE	_	100	23	10	27
8	1,4-Dioxane	_	100	23	5	55
9	Toluene	_	100	23	5	58
10	THF	_	100	23	6	74
11	DMF	_	120	3	12	83
12	DMF	_	140	3	39	40
13	DMF	_	160	3	62	0
14	DMF	_	180	0.25	60 (58)	0

^a Copper catalyst, +: with 10 mol % CuBr(PPh₃)₃, -: without copper catalyst.

^b The yield was determined by ¹H NMR using CH₂Br₂ as the internal standard. Isolated yield in parentheses.

^c 5% of (Z)-1a was recovered.

Table 2 The reaction of **1a-h**^a



Entry	1	\mathbb{R}^1	\mathbb{R}^2	R ⁴	Time (h)	3 (4)	Yield ^b (%)
1	1a	Ph	Ph	Ph	0.25	3a	58
2	1b	Ph	Ph	p-MeOC ₆ H ₄	0.25	3b	51
3	1c	Ph	Ph	$p-O_2NC_6H_4$	0.25	3c	37
4	1d	Ph	Ph	Me	0.5	3d	38
5	1e	Ph	Ph	Н	0.5	3e	12
6	1f	n-Pr	Ph	Ph	0.25	3f	56
7	1g	Су	Ph	Ph	0.25	3g	53
8	1h	Ph	n-Pr	Ph	3	3h	18
9 ^c	1h	Ph	n-Pr	Ph	7 days	(4h)	56 ^d

^a The reaction of **1** was carried out in DMF at 180 °C.

^c At 100 °C.

^d 11% of **3h** was obtained.

low yield (entry 5). Substrates **1f** and **1g** bearing an alkyl group at the alkyne terminus (\mathbb{R}^1) were effectively converted into products **3f** and **3g** in moderate yields (entries 6 and 7). In contrast, the reaction of **1h** with an alkyl substituent at the propargylic position (\mathbb{R}^2) gave the desired product in a low yield due to the decomposition of **1h** and **4h** at 180 °C (entry 8), although the reaction of **1h** at 100 °C afforded cyclic nitrone **4h** in an acceptable yield (entry 9).

As expected from the results of Table 1, when isolated **4a** was heated at 180 °C for 15 min, **3a** was obtained in 60% isolated yield, suggesting that four-membered cyclic nitrone **4** is a key intermediate to produce pyridine oxide **3** in the present reaction (Eq. 3).



A plausible mechanism for the present reaction is shown in Scheme 1. First, the thermal [2,3]-rearrangement of (*Z*)-**1** leads to *N*-allenylnitrone species **5**. Its rotamer **5**' undergoes 4π -electrocyc-lization to form four-membered cyclic nitrone **6**.⁸ The sp³-carbon-nitrogen bond is cleaved to form zwitterionic intermediate **7**. At a low reaction temperature, the re-formation of the C–N bond takes place via zwitterionic intermediate **8**, yielding another four-membered cyclic nitrone **4** having a longer conjugated chain than **6**, as the thermodynamic product at 100 °C. At a high reaction temperature, the re-formation of otcurs via



Scheme 1. Plausible mechanism.

^b Isolated yield.



Scheme 2. Electrocyclization steps in the reaction of (Z)-1 and (E)-1.



Scheme 3. [2,3]-Rearrangement process in the reaction of (Z)-1 and (E)-1.

intermediate **9**. Resulting dihydropyridine oxide **10** readily isomerizes to 2,3,6-trisubstituted pyridine oxide **3**. The reaction of **1h** at 180 °C afforded only small amounts of **3h** although corresponding cyclic nitrone **4h** was obtained in a good yield at 100 °C (Table 2, entries 8 and 9). These results suggest that the low stabilizing ability of the alkyl group at R² toward the carbocation of intermediate **8** resulted in the suppression of the cleavage of the sp³-carbonnitrogen bond of the cyclic nitrone **4h**.

The reaction of *Z* isomer (*Z*)-1 afforded 2,3,6-trisubstituted pyridine oxide, whereas that of *E* isomer (*E*)-1 produced 2,3,4,5-tetrasubstituted pyridine oxides 2 (Scheme 2, Eq. 2 versus Eq. 1). ⁴ The key to changing the substitution pattern is the geometry of the nitrone moiety in the electrocyclization step of the N-allenylnitrone intermediates 5' and 11 (Scheme 2); that is, in the latter case, the carbon-carbon double bond can be located close to the allene moiety, enabling participation in the 6π -electrocyclization, whereas in the former case, the olefinic moiety is at the opposite side, resulting in exclusive 4π -electrocyclization. Moreover, it is noteworthy that the cyclization of the Z isomer proceeds without the aid of any catalysts, whereas the E isomer requires a copper catalyst.⁹ In the [2,3]-rearrangement of (*E*)-1, the substituent \mathbb{R}^1 derived from the alkyne terminus and the substituent at the oxime moiety (R⁴–CH=CH–) approach each other (Scheme 3). To overcome the steric repulsion, the catalyst possibly generates the cyclic vinylcopper intermediate 14, which allows the rearrangement to proceed quickly. In contrast, because the substituent at the oxime moiety is located at the opposite side of \mathbb{R}^1 in the rearrangement of (*Z*)-1 to 5, as indicated in 13 as the transition state, the reaction of (Z)-1 proceeds in a concerted manner even in the absence of the catalyst.¹⁰ However, it should be noted that the copper catalyst exhibited catalytic activity in DMF at 100 °C (Table 1, entry 3 vs 5), suggesting that the cyclization process in the reaction of the Z isomer was also accelerated by the copper catalyst.

In conclusion, we have developed a new approach to the multisubstituted pyridine oxides. It should be noted that three different substituents can be substituted at the 2, 3, and 6 positions of the pyridine ring in a regiospecific manner. Further investigations of the reaction mechanism are underway in our laboratory.

Acknowledgments

This work was financially supported by a Grant-in-Aid for Scientific Research from Japan Society for Promotion in Science (JSPS).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.09.107.

References and notes

- (a) Ma, X.; Gang, D. R. Nat. Prod. Rep. 2004, 21, 752; (b) Hill, M. D. Chem. Eur. J. 2010, 16, 12052.
- For representative examples, (a) Li, N.; Wang, P.; Lai, S.-L.; Liu, W.; Lee, C.-S.; Lee, S.-T.; Liu, Z. Adv. Mater. 2010, 22, 527; (b) Yan, S.; Chen, W.; Yang, X.; Chen, C.; Huang, M.; Xu, Z.; Yeung, K. W. K.; Yi, C. Polym. Bull. 2011, 66, 1191.
- (a) Henry, G. D. Tetrahedron 2004, 60, 6043; (b) Bagley, M. C.; Glover, C.; Merritt, E. A. Synlett 2007, 2459.
- (a) Nakamura, I.; Zhang, D.; Terada, M. J. Am. Chem. Soc. 2010, 132, 7884; (b) Nakamura, I.; Zhang, D.; Terada, M. J. Am. Chem. Soc. 2011, 133, 6862.
- (a) Nakamura, I.; Araki, T.; Terada, M. J. Am. Chem. Soc. 2009, 131, 2804 (withdrawn); (b) Nakamura, I.; Araki, T.; Terada, M. J. Am. Chem. Soc. 2011, 133, 6861; (c) Nakamura, I.; Araki, T.; Zhang, D.; Kudo, Y.; Kwon, E.; Terada, M. Org. Lett. 2011, 13, 3616.
- 6. Nakamura, I.; Okamoto, M.; Terada, M. Org. Lett. **2010**, *12*, 2453.
- 7. Representative procedure for the reaction of 1. To a 3 mL pressure vial were added 1 (0.4 mmol) and DMF (0.8 mL) under argon atmosphere and the reaction mixture was stirred at 180 °C for 15–30 min. After removing the solvents in vacuo, the crude product was purified by silica gel column chromatography using hexane/ethyl acetate (1:1) as eluent to obtain 3 in an analytically pure form.
- 8. Pennings, M. L. M.; Reinhoudt, D. N. J. Org. Chem. 1982, 47, 1816.
- 9. Results of the reaction of (E)-1a;



w/ 10 mol% CuBr(PPh₃), 10mol% PPh₃, 2h, 75% NMR yield w/o Cu catalyst, 2h 10 % NMR yield [80% recovery of (*E*)-1a] (4)

 Mageswaran, S.; Ollis, W. D.; Southam, D. A.; Sutherland, I. O.; Thebtaranonth, Y. J. Chem. Soc., Perkin Trans. 1 1981, 1969.