Tetrahedron Letters 50 (2009) 4762-4765

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Development of novel pyrrole synthesis for the preparation of intermediates of bioactive pyrrole alkaloids

Eiko Yasui, Masao Wada, Norio Takamura*

Research Institute of Pharmaceutical Sciences, Musashino University, 1-1-20 Shinmachi, Nishitokyo-shi, Tokyo 202-8585, Japan

ARTICLE INFO

ABSTRACT

Article history: Received 1 May 2009 Revised 3 June 2009 Accepted 5 June 2009 Available online 7 June 2009

Keywords:

3,4-Diarylpyrrole-2,5-dicarboxylates, Piloty-Robinson pyrrole synthesis α-Diazo ester Hydrazone Polycitone Storniamide

In our series of investigations on the reactivity and the utility of α -diazo esters **1**, which are easily available from corresponding α -amino acid esters^{1,2}, we found that the terminal nitrogen of **1** was readily attacked by nucleophiles, such as aryllithiums, hydride reagents, and phosphines. The addition of aryllithiums to **1** gave aryl hydrazones **2**, the precursor for the Fisher indole synthesis.² Aryl hydrazones **2** were converted into indoles **3** under acidic conditions in good yields. Hydride reagents also reacted with **1** to yield hydrazones **4**.³ Hydrazones **4** in turn could yield 1,3,4-oxadiazin-6-ones **5**, the substrate for the Diels–Alder reaction. The terminal nitrogen of **1** also reacted with phosphines to give aza-ylides **6** that were easily hydrolyzed to furnish **4** (Fig. 1). In this Letter, we report a novel method for the synthesis of 3,4-diarylpyrrole-2,5-dicarbox-ylates **7** via **4** that were easily obtained from phenylalanine derivatives.

Several 3,4-diarylpyrrole-2,5-dicarboxylates are known for their unique biological activities. For example, polycitone A (**8**) is a natural product that inhibits the activity of retroviral reverse transcriptases and cellular DNA polymerases.⁴ Storniamide A (**10**) and permethyl storniamide A (**11**) have multidrug resistance (MDR) reversal activity⁵ (Fig. 2). The synthesis of these compounds has been performed by some groups.^{6–10} The Piloty–Robinson pyr-

* Corresponding author. Tel./fax: +81 424 68 9278.

E-mail address: noritaka@musashino-u.ac.jp (N. Takamura).



We have developed a novel method for the synthesis of 3,4-diarylpyrrole-2,5-dicarboxylates via α -diazo

esters, which are easily obtained from phenylalanine derivatives. Utilizing this method, intermediates of

bioactive compounds having the structure of 3,4-diarylpyrrole-2,5-dicarboxylates were synthesized.

role synthesis is a conventional method for the synthesis of pyrroles under vigorous reaction conditions.¹¹ The condensation of two carbonyl compounds and hydrazine gives azine **12**. It is considered that the isomerization of **12** and its subsequent cyclization furnish pyrrole **7** (Fig. 3). We speculated that hydrazones **4** obtained by our methodology from α -diazo esters **1** could be precur-





© 2009 Elsevier Ltd. All rights reserved.

^{0040-4039/\$ -} see front matter \circledcirc 2009 Elsevier Ltd. All rights reserved. doi:10.1016/j.tetlet.2009.06.012











sors for the synthesis of azine **12**. Thus, first, we exposed (*E*)-hydrazone **4a** prepared from α -diazo ester **1a** derived from ethyl phenylalaninate to acidic conditions (heating in a sealed tube with 10 mol equiv of thionyl chloride in ethanol at 90 °C for 45 min) to give azine **12a**. However, the reaction proceeded quickly and pyrrole **7a** was obtained in 94% yield instead of azine **12a** (Scheme 1).¹² (*Z*)-Hydrazone **4a**' or a mixture of both stereoisomers also gave pyrrole **7a** in good yield under the same reaction conditions.

As pyrrole **7a** was obtained in good yield, we examined other substrates (Table 1). Hydrazones **4b**–**e** derived from tyrosine derivatives gave pyrroles **7b**–**e** (entries 2–5). Protection of the hydroxyl group was not necessary for a series of reactions (diazotization, reduction, and cyclization). Although hydrazone **4f** derived from 4-chloro phenylalanine gave pyrrole **7f** in good yield, **4g** derived from 4-nitro phenylalanine failed to produce a pyrrole. Hydrazones containing 5-membered heteroaromatic compounds **4h** and **4i** were prepared from corresponding amino acid esters¹³ and subjected to cyclization. Unfortunately, no pyrroles could be obtained from these compounds.

Then, we examined the synthesis of intermediates that can lead to bioactive compounds **8**, **9**, and **11** (Scheme 2). 4-Methoxy

Table 1



Entry	Ar		R	Yield (%)
1	Ph	(4 a)	Et	94 (7a)
2	но	(4b)	Me	79 (7b)
3	MeO	(4c)	Me	79 (7c)
4	MeO MeO MeO	(4d)	Me	66 (7d)
5	BnO	(4e)	Et	74 (7e)
6	CI	(4f)	Me	80 (7f)
7	O ₂ N	(4g)	Me	0
8	Bn N N N	(4h)	Me	0
9	S S	(4i)	Me	0



Scheme 1. Reagents and conditions: (i) P(n-Bu)₃, IPE, 93%; and (ii) SOCl₂, EtOH, 90 °C (in a sealed tube).



Scheme 2. Reagents and conditions: (i) isoamyl nitrite, AcOH, CHCl₃, 70 °C; (ii) P(*n*-Bu)₃, IPE; (iii) SOCl₂, EtOH, 90 °C (in a sealed tube); (iv) aq KOH, MeOH; and (v) L-selectride[®], THF.

Table 2



ntry Conditions		Yield (%)	
1	$SOCl_2$ (×10), EtOH	94	
2	$SOCl_2$ (×5), EtOH	91	
3	$SOCl_2$ (×2.5), EtOH	63	
4	SOCI ₂ , THF	0	
5	AcCl, EtOH	84	
6	AcOH	0 ^a	
7	0.5 M ag HCl, EtOH	3	
8	36% ag HCl, EtOH	8	
9	98% H ₂ SO ₄ , EtOH	12	
10	85% H ₃ PO ₄ , EtOH	0 ^b	
11	46% HBr, EtOH	8 ^c	
12	TFA, CH ₂ Cl ₂	26	

 $^{\rm a}\,$ (Z)-Hydrazone was isolated in 19% yield. Starting material was recovered in 67% yield.

^b Starting material was recovered in 31% yield.

^c Starting material was recovered in 5% yield.

tyrosine was esterified with methanol and subjected to diazotization. The resulting diazo ester was reduced to hydrazone **4c**, and **4c** was heated in a sealed tube under acidic conditions to give pyrrole **7c** in good yield. Hydrolysis of **7c** gave corresponding carboxylic acid **13c**,¹⁴ the synthetic intermediate of **8** and **9**.^{7c} The same conversions were applied to 3,4,5-trimethoxy tyrosine obtained by known procedures¹⁵ to yield pyrrole **7d**,¹⁶ the intermediate of **11**.⁶

To clarify the mechanism of this reaction, several acidic conditions were next examined using hydrazone 4a (Table 2). We conjectured that anhydrous hydrogen chloride generated from thionyl chloride and alcohol would work as a proton source to promote the reaction. At this stage, the reaction mechanism can be represented as depicted in Figure 4. Two molecules of hydrazone 4a were condensed with the loss of hydrazine salt to yield symmetric azine 12a. Azine 12a was isomerized with the aid of acid, and 3,3-sigmatropic rearrangement led to cyclization immediately under heating with the loss of ammonium salt. When the cyclization was accomplished in THF with thionyl chloride, no pyrrole was obtained at all because no hydrogen chloride was produced. Furthermore, the combination of acetyl chloride and ethanol also gave pyrrole 7a in good yield. Although hydrogen chloride seemed to be an essential factor, aqueous hydrochloric acid hardly promoted the reaction (entries 7 and 8). Also, sulfuric acid and phosphoric acid were not suitable (entries 9 and 10). Acetic acid promoted only the isomerization of the hydrazone 4a to give 4a' in 19% yield, and 67% of the starting material was recovered. Hydrobromide in acetic acid produced a small amount of pyrrole **7a**. Thus, the combination of thionyl chloride and alcohol is the best condition. Although the yield scarcely decreased when the amount of thionyl chloride was reduced to 5 mol equiv (91%), use of 2.5 mol equiv of thionyl chloride severely lowered the yield (63%). Further studies aimed at developing a novel method for the synthesis of pyrroles from other α -diazo esters derived from a variety of α -amino acid esters are in progress.

In conclusion, we have developed a novel method for the synthesis of 3,4-diarylpyrrole-2,5-dicarboxylates via α -diazo esters that are easily obtained from phenylalanine derivatives. Our method is milder than the Piloty–Robinson pyrrole synthesis, and pyrroles are obtained in good yields.



Figure 4.

Acknowledgments

This work was financially supported by MEXT. HAITEKU (2008) and the Uehara Memorial Foundation (2008).

References and notes

- 1. (a) Takamura, N.; Mizoguchi, T.; Koga, K.; Yamada, S. Tetrahedron Lett. 1971, 12, 4495-4498; (b) Takamura, N.; Mizoguchi, T.; Koga, K.; Yamada, S. Tetrahedron 1975, 31, 227-230.
- (a) Yasui, E.; Wada, M.; Takamura, N. Tetrahedron Lett. 2006, 47, 743-746; (b) Yasui, E.; Wada, M.; Takamura, N. Tetrahedron 2009, 65, 461–468.
- Yasui, E.; Wada, M.; Takamura, N. Chem. Pharm. Bull. 2007, 55, 1652-3. 1654.
- (a) Rudi, A.; Goldberg, I.; Stein, Z.; Frolow, F.; Benavahu, Y.; Schlever, M.; 4 Kashman, Y. J. Org. Chem. **1994**, 59, 999–1003; (b) Rudi, A.; Evan, T.; Aknin, M.; Kashman, Y. I. Nat. Prod. 2000, 63, 832-833.
- 5 Palermo, I. A.; Rodriguez Brasco, M. F.; Seldes, A. M. Tetrahedron 1996, 52. 2727-2734.
- 6. Boger, D. L.; Boyce, C. W.; Labroli, M. A.; Sehon, C. A.; Jin, Q. J. Am. Chem. Soc. 1999. 121. 54-62.
- (a) Terpin, A.; Polborn, K.; Steglich, W. Tetrahedron 1995, 51, 9941-9946; (b) 7 Ebel, H.; Terpin, A.; Steglich, W. Tetrahedron Lett. **1998**, 39, 9165–9166; (c) Kreipl, A. T.; Reid, C.; Steglich, W. Org. Lett. **2002**, 4, 3287–3288.
- 8
- (a) Gupton, J. T.; Miller, R. B.; Krumpe, K. E.; Clough, S. C.; Banner, E. J.; Kanters, R. P. F.; Du, K. X.; Keertikar, K. M.; Lauerman, N. E.; Solano, J. M.; Adams, B. R.; Callahan, D. W.; Little, B. A.; Scharf, A. B.; Sikorski, J. A. Tetrahedron 2005, 61, 1845–1854; (b) Gupton, J. T.; Banner, E. J.; Sartin, M. D.; Coppock, M. B.; Hempel, J. E.; Kharlamova, A.; Fisher, D. C.; Giglio, B. C.; Smith, K. L.; Keough, M. J.; Smith, T. M.; Kanters, R. P. F.; Dominey, R. N.; Sikorsky, J. A. Tetrahedron 2008, 64. 5246-5253.

- 10. (a) Iwao, M.: Takeuchi, T.: Fujikawa, N.: Fukuda, T.: Ishibashi, F. Tetrahedron Lett. 2003, 44, 4443–4446; (b) Fukuda, T.; Hayashida, Y.; Iwao, M. Heterocycles 2009, 77, 1105-1122.
- (a) Piloty, O. Ber. 1910, 43, 489-498; (b) Robinson, G. M.; Robinson, R. J. Chem. 11 Soc. 1918, 113, 639-645.
- 12. Typical experimental procedure for the synthesis of pyrrole 7a: Hydrazone 4a (176.1 mg, 0.85 mmol) was dissolved in ethanol (2 mL) in a sealed tube. To this solution, thionyl chloride (0.62 mL, 8.50 mmol) diluted in ethanol (3 mL) was slowly added at 0 °C, and the mixture was stirred for 45 min at 90 °C. After cooling to room temperature, the reaction mixture was slowly poured into saturated NaHCO₃ (30 mL) and extracted with ethyl acetate (10 mL) thrice. The organic phase was dried over Na₂SO₄ and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/ ethyl acetate = 3:1) to give 7a as colorless crystals (145.5 mg, 94%). Recrystallization from ethyl acetate and hexane afforded colorless needles, mp (151-151.8 °C). Data for **7a**: ¹H NMR (400 MHz, CDCl₃) δ 9.86 (br s, 1H), 7.21 7.16 (m, 6H), 7.15–7.19 (m, 4H), 4.22 (q, 4H, J = 8.0 Hz), 1.17 (t, 6H, J = 8.0 Hz); ¹³C NMR (100 MHz, CDCl₃) & 160.55, 133.14, 131.46, 130.93, 127.34, 127.00, 121.64, 60.97, 14.09; IR (KBr) 3325, 1703, 1302, 1242 cm⁻¹; HRMS (EI) calcd for C₂₂H₂₁NO₄ (M⁺) 363.1471, found 363.1477
- Himes, R. A.; Park, G. Y.; Barry, A. N.; Blackburn, N. J.; Karlin, K. D. J. Am. Chem. 13 Soc. 2007, 129, 5352-5353.
- The spectral data for **13c** exhibited properties that were identical to those reported by Gupton et al.^{9b} Data for **13c**: mp 199–200.5 °C (DMSO) (lit.^{9b} 200– 14 202 °C); ¹H NMR (400 MHz, DMSO- d_6) δ 11.58 (br s, 1H), 6.92 (d, J = 8.0 Hz, 4H), 6.69 (d, J = 8.0 Hz, 4H), 3.68 (s, 6H); ¹³C NMR (100 MHz, DMSO- d_6) δ 162.01, 158.25, 132.31, 130.23, 126.54, 122.66, 113.12, 55.36; IR (KBr) 3413, 1675, 1245 cm⁻¹; HRMS (EI) calcd for C₂₀H₁₇NO₆ (M⁺) 367.1056, found 367.1054.
- Dauzonne, D.; Royer, R. Synthesis 1987, 399-401.
- The spectral data for 7d exhibited properties that were identical to those reported by Boger et al.⁶ Data for 7d: mp 168.0-168.5 °C (CHCl₃-hexane) (lit.⁶ 153-155 °C); ¹H NMR (400 MHz, CDCl₃) δ 9.85 (br s, 1H), 6.36 (s, 4H), 3.81 (s, 12H), 3.64 (s, 12H); ¹³C NMR (100 MHz, CDCl₃) & 160.71, 152.44, 137.34, 131.22, 128.19, 121.10, 108.50, 60.98, 56.15, 52.04; IR (KBr) 3276, 2942, 1702, 1239, 1125 cm⁻¹; HRMS (EI) calcd for C₂₆H₂₉NO₁₀ (M⁺) 515.1791, found 515.1750.