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Tetrahedron Letters 45 (2004) 3953–3955
Tetrahedron Letters

Synthesis of polysubstituted dihydropyrroles and pyrroles from β-carbonyl *O*-methyloximes

Zhiquan Song, John Reiner and Kang Zhao*

College of Pharmaceuticals and Biotechnology, Tianjin University, Tianjin 300072, China

Received 26 December 2003; revised 2 March 2004; accepted 11 March 2004

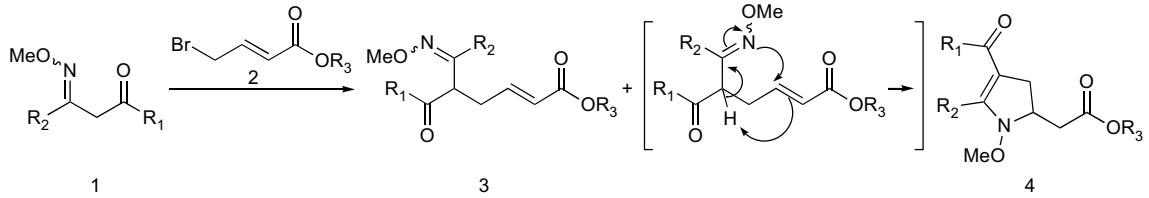
Abstract—Polysubstituted 4,5-dihydropyrroles and pyrroles were synthesized from β-carbonyl *O*-methyloximes via alkylation and intramolecular Michael addition with unsaturated 4-bromobutyrates by treatment with sodium hydride or a sodium alkoxide.

Since the pyrrole subunit occurs in many medicines, pesticides, and natural products, the development of new methodologies[1–4] for the synthesis of pyrroles is of interest. However, few of these methods involve β-carbonyl *O*-methyloximes as precursors of the pyrrole system. In this paper we report a new method to synthesize polysubstituted 4,5-dihydropyrroles and pyrroles starting from readily available β-carbonyl *O*-methyloximes.

The required β-carbonyl *O*-methyloximes were prepared by two different methods. *O*-Methyloximes of acetylacetone and ethyl acetoacetate were easily obtained by reaction with 1 equiv of *O*-methylhydroxylamine. In a second method,[5] *O*-methyloximes (**1**, $R_1 = n$-Pr, *i*-Pr, Ph, 2-furyl) were synthesized from acetone *O*-methyloxime. The mixtures of *E*- and *Z*-isomers were utilized without further separation.

Upon reaction of β-carbonyl *O*-methyloximes with 4-bromocrotonates (**2**), prepared by the bromination of crotonates with NBS and AIBN in high yields,[6] two main products resulted, either the alkylation product **3** or after further cyclization, the dihydropyrrole **4**. Product ratios varied depending on the starting oxime. When $R_1 =$ Me, EtO, Ph, or 2-furyl, 4,5-dihydropyrrole **4** was the predominant product (Scheme 1); whereas, when $R_1 = n$-Pr or *i*-Pr, compound **3** was the predominant product. For the *O*-methyloximes of ethyl benzoylacetate and ethyl butyrylacetate,[7] the predominant products were the branched chain compounds (**3**), and not the intramolecular Michael addition products **4**.

After optimization, two methods were adopted to synthesize 4,5-dihydropyrroles in a single step. Method A: to an alcohol solution of sodium alkoxide (1.05 equiv), *O*-methyloxime (1 equiv) was added dropwise. After stirring for 30 min at ambient temperature, 4-bromocrotonate (1 equiv) was added, followed by reflux for 1.5 h. Method B: to a DMF solution of *O*-methyloxime (1 equiv), sodium hydride (1 equiv) was added portionwise. After stirring for 30 min at ambient temperature,



Scheme 1.

* Corresponding author. Tel.: +86-22-2740-4031; fax: +86-22-2789-0968; e-mail: combinology@yahoo.com

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.03.115

4-bromocrotonate (1 equiv) was added, followed by stirring for 2 h at ambient temperature. The product was extracted into ethyl acetate and was purified by silica gel chromatography (AcOEt–petroleum ether = 1:9). Results of the reactions are listed in Table 1.

In an analogous manner, β-carbonyl *O*-methyloximes were treated with methyl 4-bromo-2-butenoate (**5**),[8,9] prepared from propargyl alcohol, to afford pyrroles in one step (Scheme 2). For this transformation, NaH was the preferred base compared with MeONa, K_2CO_3, DBU, or Et_3N, and DMF was the preferred solvent as compared to MeOH, THF, or CH_2Cl_2, probably because of its polarity. The reaction was conducted according to method B. The results are listed in Table 2.

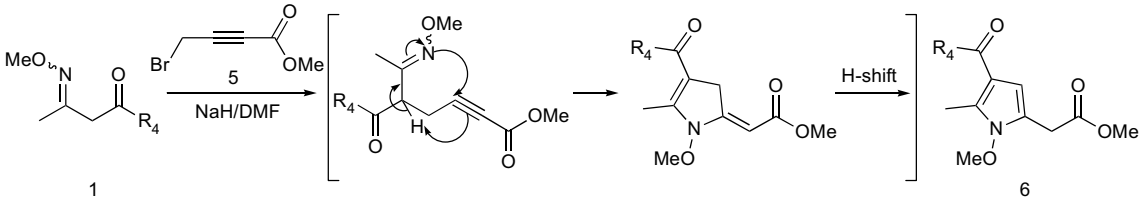
To verify that the pyrrole and not a furan was the reaction product, the furan was prepared by an independent synthesis (Scheme 3). Moubarak, et al.[10] have reported a preparation of 2,4,5-trisubstituted furans by the reaction of active methylene compounds such as acetylacetone and ethyl acetoacetate with ethyl 3,4-dibromo-2-butenoate. Similarly, compound **7** was prepared by the reaction of acetylacetone and methyl 4-bromo-2-butenoate in the presence of potassium carbonate. *O*-Methyloxime **8** was obtained after the reaction with *O*-methylhydroxylamine in DMF at 80 °C (Scheme 4). Compound **6a** clearly differed from *O*-methyloxime **8** in the ^{1}H NMR spectra with a chemical shift for the pyrrole C-4 proton at 7.18 ppm, versus 6.36 ppm for the corresponding furan C-4 proton.

In addition, an interesting ring interconversion reaction from a dihydrofuran ring to a dihydropyrrole ring was observed when *O*-methyloxime **10** was treated with base (Scheme 4). According to the literature,[11,12] compound **9** was the main product when acetylacetone was reacted with methyl 4-bromocrotonate. The oximation of **9** was carried out with *O*-methylhydroxylamine hydrochloride and triethylamine in DMF at 80 °C in 82% yield. By TLC and ^{1}H NMR, bases like DBU and *t*-BuOK afforded the ring conversion reaction. The predominant

Table 1. Data for 4,5-dihydropyrroles

Compound	R_1	R_2	R_3	Method	Yield[a] [%]	^{1}H NMR ($CDCl_3$/TMS) δ [ppm]
4a	Me	Me	Me	A	55	3.90–3.86 (m, 1H); 3.64 (s, 3H); 3.62 (s, 3H); 2.84–2.77 (m, 2H); 2.46 (q, 1H, $J = 8.0$ Hz); 2.31–2.25 (m, 1H); 2.16 (s, 3H); 2.10 (s, 3H)
4b	EtO	Me	Et	B	45	4.13–4.07 (m, 4H); 3.84–3.81 (m, 1H); 3.63 (s, 3H); 2.82–2.76 (m, 2H); 2.47 (q, 1H, $J = 8.0$ Hz); 2.25–2.19 (m, 1H); 2.15 (s, 3H); 1.23–1.19 (m, 6H)
4c	Ph	Me	Me	A	42	7.53–7.52 (m, 2H); 7.45–7.35 (m, 3H); 4.04–3.99 (m, 1H); 3.67 (s, 6H); 2.98–2.92 (m, 1H); 2.89–2.84 (m, 1H); 2.55 (q, 1H, $J = 8.0$ Hz); 2.49–2.44 (m, 1H); 1.86 (s, 3H)
4d	2-Furyl	Me	Me	A	62	7.47 (s, 1H); 7.03–7.01 (m, 1H); 6.44–6.42 (m, 1H); 4.03–4.00 (m, 1H); 3.67–3.66 (m, 6H); 3.19–3.16 (m, 1H); 2.88–2.83 (m, 1H); 2.69–2.66 (m, 1H); 2.56–2.50 (m, 1H); 2.25 (s, 3H)

[a] Isolated yield.

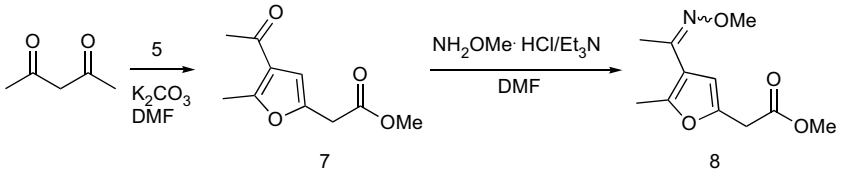


Scheme 2.

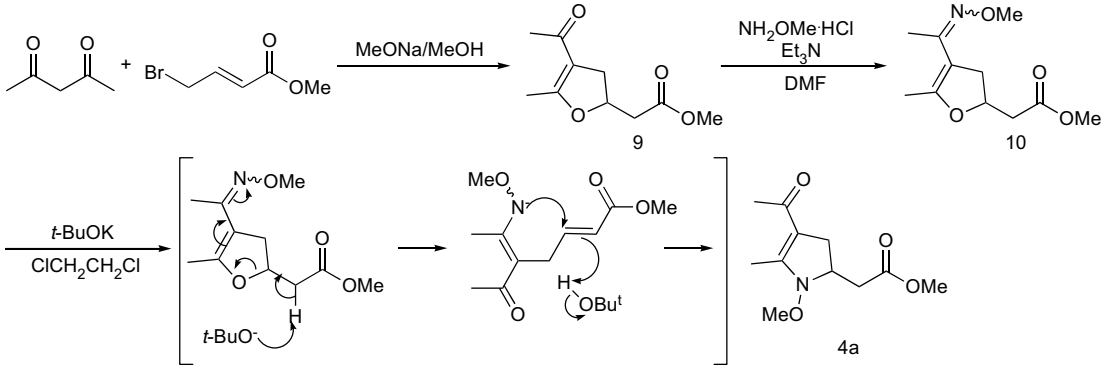
Table 2. Data for pyrroles

Compound	R_4	Yield[a] [%]	^{1}H NMR ($CDCl_3$/TMS) δ [ppm]
6a	Me	25	7.18 (s, 1H); 3.86 (s, 3H); 3.65 (s, 3H); 3.50 (s, 2H); 2.34 (s, 3H); 2.08 (s, 3H)
6b	EtO	29	6.61 (s, 1H); 4.18 (q, 2H, $J = 7.2$ Hz); 3.90 (s, 3H); 3.65 (s, 3H); 3.64 (s, 2H); 2.43 (s, 3H); 1.26 (t, 3H, $J = 7.2$ Hz)
6c	$CH_3CH_2CH_2$	33	7.21 (s, 1H); 3.83 (s, 3H); 3.66 (s, 3H); 3.50 (s, 2H); 2.63 (t, 2H, $J = 7.6$ Hz); 2.08 (s, 3H); 1.67–1.62 (m, 2H); 0.90 (t, 3H, $J = 7.2$ Hz)
6d	$(CH_3)_2CH$	30	7.21 (s, 1H); 3.88 (s, 3H); 3.65 (s, 3H); 3.48 (s, 2H); 3.12–3.05 (m, 1H); 2.08 (s, 3H); 1.23–1.19 (m, 6H)
6e	Ph	51	7.53–7.51 (m, 2H); 7.45 (s, 1H); 7.37–7.34 (m, 2H); 7.29–7.27 (m, 1H) 3.86 (s, 3H); 3.69 (s, 3H); 3.41 (s, 2H); 2.01 (s, 3H)
6f	2-Furyl	52	7.43 (s, 1H); 7.35 (s, 1H); 6.59–6.58 (m, 1H); 6.45–6.43 (m, 1H); 3.92 (s, 3H); 3.68 (s, 3H); 3.55 (s, 2H); 2.05 (s, 3H)

[a] Isolated yield.



Scheme 3.



Scheme 4.

Table 3. Data for furans and 4,5-dihydrofuran

Compound	Yield[a] [%]	^{1}H NMR δ [ppm]
7[b]	40	6.57 (s, 1H); 3.73 (s, 2H); 3.61 (s, 3H); 2.46 (s, 3H); 2.31 (s, 3H)
8[b,c]	70	6.36 (s, 1H); 3.80 (s, 3H); 3.68 (s, 2H); 3.61 (s, 3H); 2.35 (s, 3H); 2.01 (s, 3H)
9	81	5.07–4.97 (m, 1H); 3.73 (s, 3H); 3.20–3.12 (m, 1H); 2.78 (q, 1H, $J = 7.5$ Hz); 2.68–2.61 (m, 2H); 2.21 (s, 6H)
10[c]	82	4.92–4.87 (m, 1H); 3.85 (s, 3H); 3.72 (s, 3H); 3.10–3.02 (m, 1H); 2.74 (q, 1H, $J = 7.5$ Hz); 2.60–2.52 (m, 2H); 2.02 (s, 6H)

[a] Isolated yield.
[b] ^{1}H NMR in DMSO-d_6/TMS, others were in $CDCl_3$/TMS.
[c] The major isomer.

product, the same as compound **4a** by ^{1}H NMR, was isolated in 50% yield (Table 3).

In conclusion, we have synthesized a series of polysubstituted 4,5-dihydropyrroles and pyrroles from β-carbonyl *O*-methyloximes by a convenient method, which may be extended to the synthesis of dihydropyrrole or pyrrole libraries.

Acknowledgements

K.Z. acknowledges the Outstanding Young Scholarship from NSFC (#30125043), the Basic Research Project (#2002CCA01500) of the MOST and the Cheung Kong Scholars Programme for the financial supports.

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