ORGANIC LETTERS

2009
Vol. 11, No. 19
4282−4285

A Direct Preparation of N-Unsubstituted Pyrrole-2,5-dicarboxylates from 2-Azidocarboxylic Esters

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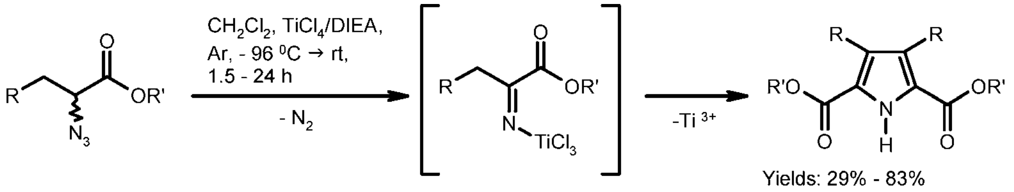
Received July 17, 2009

ABSTRACT



A new and easy method for synthesis of symmetric pyrrole-2,5-dicarboxylate derivatives via a simple titanium(IV)-mediated oxidative dimerization of 2-azidocarboxylic esters is described. The process involves a transformation of titanium(IV) enolates into nonisolated 2-iminoesters, which undergo an oxidative coupling and ring closure to give the aromatic pyrrole system. A mechanism, scope and limitations of the new method are discussed.

Pyrrole-2,5-dicarboxylates have many applications in various fields of medicinal and bioorganic chemistry, phytochemistry, and materials science and as building blocks for synthesis of chiral catalysts and natural products. The 3,4-diaryl-substituted pyrrole ring bearing 2,5-dicarboxylates is a structural subunit found in marine natural products ningalin A and storniamide A, which are precursors of cytotoxic antitumor agents.[1] Similarly, the pyrrole-2,5-dicarboxylate core has been indicated in chromopyrrolic acid (CPA), which is the key intermediate of biosynthesis of cytotoxic indolocarbazoles[2] and in some bisindole alkaloids isolated from *Arcyria cinerea* and *Lycogala epidendrum*.[3] Symmetrical 3,4-disubstituted pyrrole-2,5-dicarboxylates have found utility in the preparation of modified porphyrins[4] and as useful precursors of novel chiral ancillary ligands designed for molecular catalysis.[5] Some amide and thioamide derivatives of the 1*H*-pyrrole-2,5-dicarboxylic acid have been synthesized and investigated as a new group of neutral anion receptors because of their complexation properties.[6] In the past decade, a very intensive exploration of pyrrole-2,5-dicarboxylic acid derivatives has been observed in the area of research on self-assembling systems and self-organization processes, development of novel “intelligent” materials with tailor-made properties, and the search for new self-folding molecules.[7]

The growing interest in the applications and efficiency of 1*H*-pyrrole-2,5-dicarboxylate derivatives has led to two main synthetic approaches.[8] Simple, unsubstituted at C-3 and C-4 1-*H*-pyrrole-2,5-dicarboxylates are prepared directly from

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(1) Boger, D. L.; Boyce, C. W.; Labroli, M.; Sehon, C. A.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 54–62.

(2) Howard-Jones, A.; Walsh, C. T. *J. Am. Chem. Soc.* **2007**, *129* (36), 11016–11017.

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(6) (a) Zielinski, T.; Jurczak, J. *Tetrahedron* **2005**, *61*, 4081–4089. (b) Dobrzycki, L.; Zielinski, T.; Jurczak, J.; Wozniak, K. *J. Phys. Org. Chem.* **2005**, *18*, 864–869.

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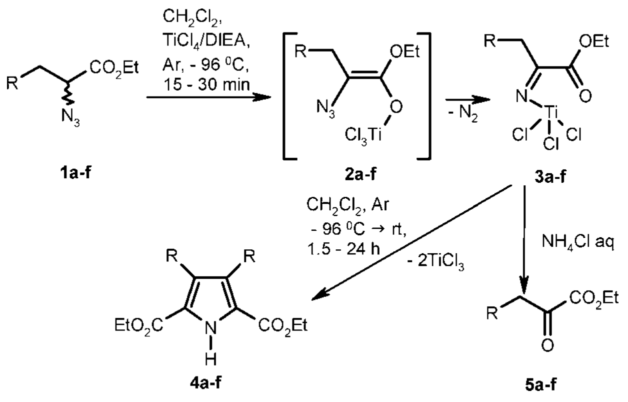
10.1021/ol901637w CCC: $40.75

pyrrole[6a,7b,9,10] in multistep processes. An approach to 3,4-disubstituted pyrrole-2,5-dicarboxylates consists in de novo ring construction applying reductive ring contraction of 1,2-diazines prepared in azadiene Diels−Alder reactions,[1] transformation of 1*H*-pyrrolo-3,4-dialkyl-5-methyl-2-carboxylates derived from 3-substituted 2,4-pentanediones,[11] or using the Paal−Knorr reaction of anilines with 2,5-dihydroxyhexa-2,4-dienedioic acid diethyl ester.[7a] The last procedure is limited to only N-substituted pyrrole-2,5-dicarboxylates. All of the mentioned methods lead to designed pyrrole-2,5-dicarboxylate derivatives in long, multistep syntheses.

In 1999, Periasamy reported a simple procedure for preparation of some N-substituted 2,5-diarylpyrroles from aromatic ketimines[12] via titanium(IV) enamines, but the method is limited only to ketimines generated from arylmethyl ketones.

In our research, we focused on the oxidative coupling of titanium(IV) enolates derived from 2-azidocarboxylic esters. Titanium(IV) enolates were obtained in accordance with the method described by Matsumura.[13] The titanium(IV) enolates of 2-azidoesters **2** are very unstable and undergo an intensive nitrogen extrusion[14] even below −80 °C to give intermediate titanium(IV) complexes of 2-iminoesters **3**. The nonisolable complexes **3** undergo smooth transformation into 3,4-disubstituted 1-*H*-pyrrole-2,5-dicarboxylates **4** (Table 1).

Table 1. Yields, Conditions, and Reaction Time for Transformations of Ethyl 2-Azidocarboxylates **1a−f**



entry	R	reaction time[a] (h)	yield (%) of **4**
a	H	1.5	83
b	CH_3	2.5	76
c	C_2H_5	4.0	68
d	C_3H_7	5.0	75
e	C_5H_{11}	6.4	55
f	$C_{13}H_{27}$	24	29

[a] After addition of DIEA.

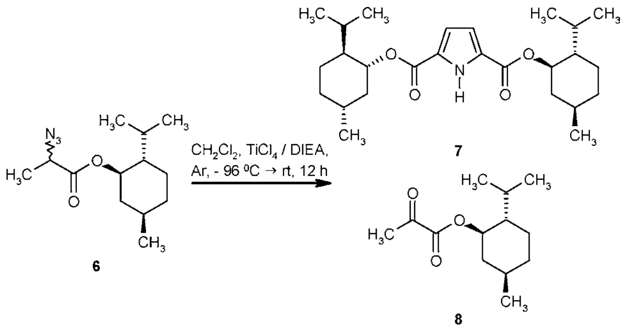
Monitoring of the reaction with gas chromatography leads to the conclusion that the conversion of 2-azidoesters **1** into pyrrole-2,5-dicarboxylate derivatives **4** is a three-step process. The first fast step consists in the transformation of 2-azidoester **1** to the appropriate 2-iminoester **3**. Then the intermediate **3** can be indicated in a gas chromatogram as 2-ketoester **5** owing to a hydrolytic workup of the sample isolated from the reaction mixture.

The second slow step is an oxidative coupling of the 2-iminoester **3** followed by very rapid heterocyclization. Concentration of the final product, 1-*H*-pyrrole-2,5-dicarboxylate derivative **4**, increases, while the quantity of the appropriate 2-iminoester **3** is gradually decreased (see the Supporting Information).

The total time needed for a complete conversion depends on the chemical structure of the starting 2-azidoester. Ethyl 2-azidopropionate **1a** is fully transformed into pyrrole-2,5-dicarboxylate **4a** in 2 h, but the similar reaction of ethyl 2-azidopalmitate **1f** needs 24 h and gives a mixture of pyrrole-2,5-dicarboxylate **4f** and ethyl 2-ketohexadecanoate **5f**.

Similarly, L-menthyl 2-azidopropionate **6** can be transformed into pyrrole-2,5-dicarboxylate **7** within 12 h, but the reaction mixture includes also L-menthyl pyruvate **8** as a byproduct. A bulky ester group has no influence on conversion of 2-azidocarboxylate into 2-iminoester but makes the oxidative dimerization slower (Scheme 1).

Scheme 1. Conversion of L-Menthyl 2-Azidopropanoate **6** to Pyrrole-2,5-dicarboxylate **7** and L-Menthyl Pyruvate **8**



An analysis of the results makes an assumption that the oxidative coupling of 2-azidocarboxylates strongly depends on the substituents at the C-3 carbon atom. A reaction of ethyl 2-azidoisovalerate **9** having a tertiary carbon atom C-3, with titanium(IV) chloride and DIEA, can be the confirmation of this hypothesis. GC−MS spectra of the reaction mixture show that the process stopped after formation of 2-iminoester **10** and there are no traces of the oxidative coupling products (Scheme 2) including the open-chain intermediate **11**. This experiment proved that the oxidative

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(9) Matsuki, S.; Mizuno, A.; Annoura, H.; Tatsuoka, T. *J. Heterocycl. Chem.* **1997**, *34*, 87.

(10) Barker, P.; Gendler, P.; Rappoport, H. *J. Org. Chem.* **1978**, *43*, 4849–4853.

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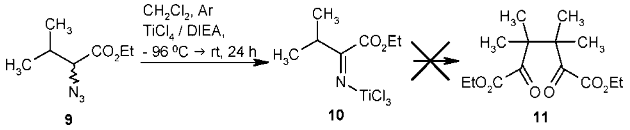
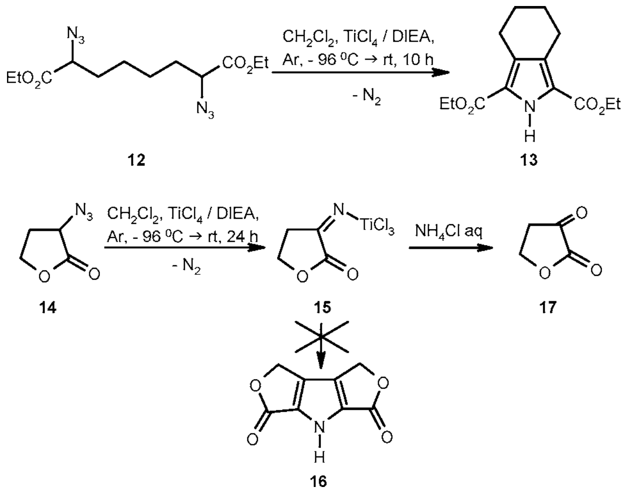
Scheme 2. Reaction of Ethyl 2-Azido-3-methylbutanoate (Ethyl 2-Azidoisovalerate) **9** with $TiCl_4$−DIEA Oxidizing System



coupling of 2-azidoesters was limited to reactants having a primary or secondary carbon atom C-3.[15]

Successful syntheses of simple 1*H*-pyrrole-2,5-dicarboxylates **4** prompted us to the construction of fused heterocyclic systems with a pyrrole substructure in a one-pot reaction. The first reactant chosen, 2,9-diazidooctanedioic acid diethyl ester **12**, was a potential precursor of 4,5,6,7-tetrahydro-2*H*-isoindole-1,3-dicarboxylic acid diethyl ester **13**. In fact, oxidative coupling of diester **12** gave isoindole derivative **13** in good yield within 10 h (Scheme 3).

Scheme 3. Synthesis of Fused Pyrrole Derivatives

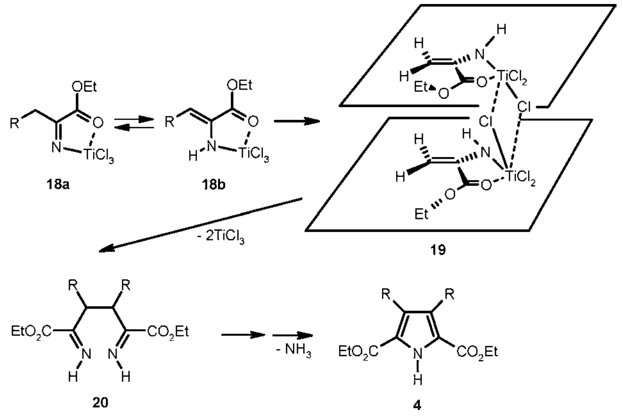


Unfortunately, the same procedure applied for the heterocyclic 2-azido-γ-butyrolactone **14** fails. Instead of the desired 4,7-dihydro-1*H*-difuro[3,4-*b*;3′,4′-*d*]pyrrole-3,5-dione **16**, only dihydrofuran-2,3-dione **17** is isolated as the main product.

A mechanism of the nitrogen elimination from titanium(IV) enolates of 2-azidoesters has not been yet investigated. It seems that this process should be analogous to that described previously by Takeuchi[16] for decomposition of aryl azides in the presence of $AlCl_3$. The titanium(IV) complexes of 2-azidoesters are stable, and any symptoms of their decomposition are not observed in the absence of a tertiary amine. Their conversion to 2-iminoesters begins rapidly when the amine is added to the reaction mixture. The crucial role of the amine consists probably in the transformation of the titanium(IV) complex into very unstable titanium(IV) enolate **2** that loses a molecular nitrogen to give the 2-imino ester **3**.

Our mechanistic proposal for the oxidative coupling of 2-imino esters **18** is based on tentative mechanisms proposed by Matsumura[17] and Periasamy.[12] Matsumura[17] postulates formation of a dimeric transition state as a key step during oxidative dimerization of phenylacetates. This model explains the high *dl*-stereoselectivity of the dimerization process. Analysis of the oxidative coupling of 2-iminoesters leads to the conclusion that the starting reactive intermediate is titanium(IV) enamine **18b** rather then imine titanium(IV) complex **18a**. The titanium(IV) enamine **18b** undergoes an oxidative coupling in a manner similar to that of aryl acetates, via dimeric transition state **19**, to give the open-chain 1,4-diimine **20**. Cyclization and aromatization of **20** leads to 1*H*-pyrrole 2,5-dicarboxylate system **4** (Scheme 4).

Scheme 4. Depicted Mechanism of an Oxidative Dimerization of the Intermediate 2-Iminocarboxylates



The observed correlations between chemical structure of the starting 2-azidocarboxylates and their reactivity indicates an appearance of the dimeric transition state during oxidative couplings of iminoesters. Moreover, it seems that the formation of the dimeric titanium(IV) enolates is a typical process preceding an oxidative formation of a single carbon−carbon bond. Limitations of the described method could result from steric hindrance occurring when the transient dimer is formed. Oxidative dimerization of L-menthyl 2-azidopropionate into di-L-menthyl 1*H*-pyrrole-2,5-dicarboxylate **7** is possible because both large ester groups are able to assume distant positions to each other. In the case of 2-azido-γ-butyrolactone **14**, the

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(12) Periasamy, M.; Srinivas, G.; Bharathi, P. *J. Org. Chem.* **1999**, *64* (11), 4204–4205.

(13) Matsumura, Y.; Nishimura, M.; Hiu, H.; Watanabe, M.; Kise, N. *J. Org. Chem.* **1996**, *61*, 2809–2812, and references therein.

(14) An elimination of the molecular nitrogen from 2-azidocarboxylates has been previously reported by Manis and Rathke only for lithium enolates of 2-azido esters. The authors exploited this instability of 2-azido esters under basic conditions in a new approach to 2-keto esters. For more information, see: Manis, P. A.; Rathke, M. W. *J. Org. Chem.* **1980**, *45* (24), 4952–4954.

(15) These results are in accordance with those reported earlier for the oxidative coupling of 2-isotiocyanatocarboxylates and strongly supported the mechanism being characterized by dimeric transition state, firstly proposed by Matsumura for oxidative coupling of phenylacetates. See also: Cież, D. *Tetrahedron* **2007**, *63*, 4510–4515.

(16) Takeuchi, H.; Maeda, M.; Mitani, M.; Koyama, K. *J. Chem. Soc., Perkin Trans. 1* **1987**, 57.

dimeric transition state **21** is unfavorable owing to strong steric repulsions between the hydrogen atoms bound to methylene groups (as illustrated in Figure 1). Similarly, the substitution of the C-3 carbon in 2-azidocarboxylates with three groups causes such strong steric strains around the crowded dimeric titanium(IV) intermediate that the oxidative coupling is inhibited.

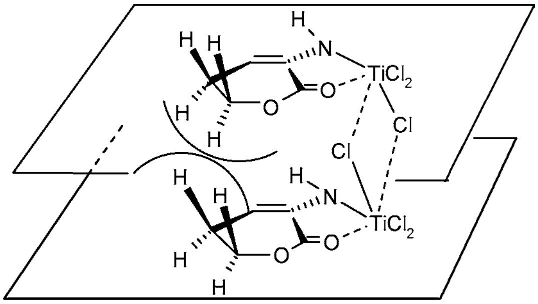

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Figure 1. Illustration of the steric repulsions during formation of the dimeric intermediate.

In conclusion, we have discovered an easy and very efficient method for preparation of symmetrical 3,4-disubstituted 1*H*-pyrrole-2,5-dicarboxylates from esters of 2-azidocarboxylic acids. The new procedure has also been developed for synthesis of isoindole derivatives, and we believe this method could be exploited for preparation of numerous fused pyrrole-2,5-dicarboxylates. Investigation of the reaction mechanism led us to the conclusion that the dimeric transition state was a common intermediate for oxidative couplings of titanium(IV) enolates and also titanium(IV) enamines.

Acknowledgment. I gratefully acknowledge the financial support of the Ministry of Science and Higher Education (Grant No. N N204 310037).

Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org

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(17) Matsumura, Y.; Kise, N.; Tokioka, K.; Aoyama, Y. *J. Org. Chem.* **1995**, *60*, 1100–1001.