A new route to non-natural aryl-containing amino acids and their precursors from thiophenes

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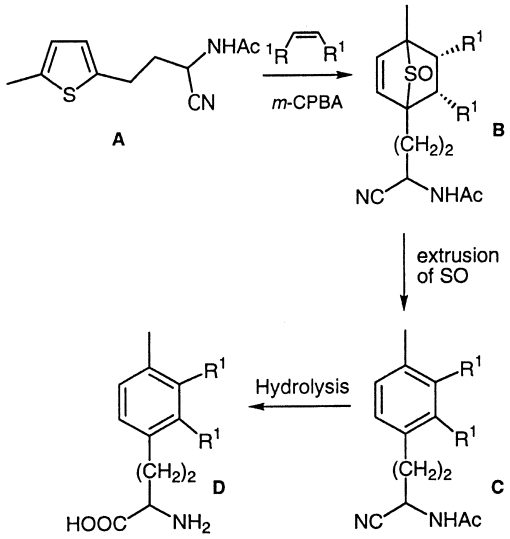
Thiophenes may be converted to substituted arenes by oxidative cycloaddition to alkynes or by oxidative cycloaddition to alkenes with subsequent oxidative SO-extrusion. Cyano- and acetylamino-groups do not interfere in the reaction and are stable under the reaction conditions. This transformation can be used as a novel route to non-natural aryl-containing amino acids.

Keywords: amino acid, thiophene, thiophene *S*,*S*-dioxide, thiophene *S*-oxide, cycloaddition, oxidation

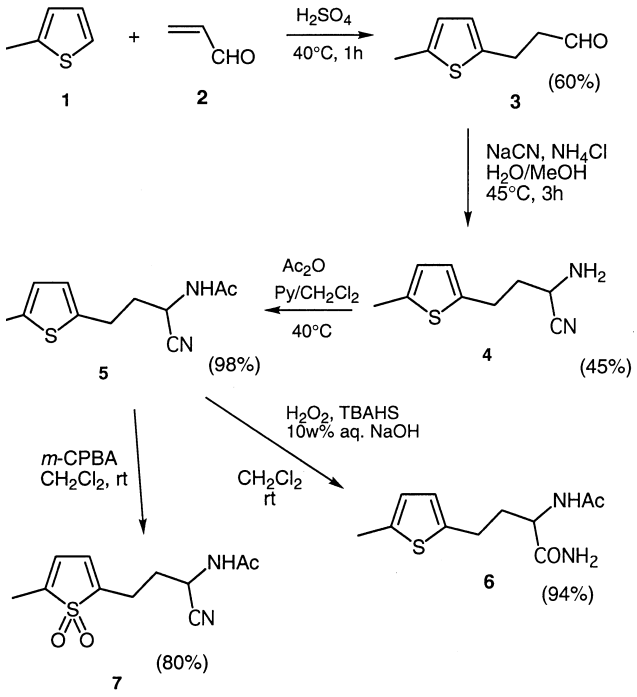
New routes to novel amino acids are still of interest.[1] New phenylalanine derivatives find use in such diverse fields as pharmacology,[4,5] fine chemical development in the area of photoaffinity labelling[6] and in materials science as building blocks for the construction of non-linear optical material.[7] We present a new route to aryl-containing amino acids, which is based on the cycloaddition of an oxidised thiophene as the key step. The key step makes it possible to derivatise the molecules at a late stage of the synthesis. The thiophene carries functionalities which can be transformed to an amino- and a carboxyl function in the last step of the preparative sequence (Scheme 1).



Scheme 1

In general, thiophenes themselves, as heteroaromatic compounds, are not very reactive towards cycloaddition reactions. With the oxidation of the sulfur, the molecules lose their heteroaromatic character and are much more prone to [4 + 2]-cycloadditions. While the thiophene *S*,*S*-dioxides still require higher reaction temperatures, thiophene *S*-oxides, which are formed intermittently in the peracid mediated oxidation of thiophenes to thiophene *S*,*S*-dioxides, are much more reactive. While some thiophene *S*-oxides can be isolated, they can also be reacted *in situ* as the diene component in cycloaddition reactions.[8,10]

The known thienylcarbaldehyde **3**[11] can be converted in a Strecker synthesis to **4**. The amino group in **4** is protected as the *N*-acetyl derivative in order to render it unreactive in the subsequent oxidation of the thiophene (Scheme 2).



Scheme 2

Compound **5** was then oxidised with *meta*-chloroperoxybenzoic acid in the presence of electron-poor alkenes to produce cycloadducts such as **8** and **11** (Scheme 3). The reactive species in these reactions are thought to be the corresponding thiophene *S*-oxides. The cycloadducts are produced as two diastereoisomers, where the cycloaddition does not control the stereocenters formed in the reaction in relation to the stereocenter at the methine carbon α to the acetylamino and cyano functions. The stereochemical relationship of the stereocentres which are formed is fixed. The cycloadducts are *endo*-products and the stereocenter at sulfur is governed by the Cieplak effect.[8,22,23] The oxygen atom of the sulfoxy group points in the direction of the ring-annelated moiety. We did not attempt to separate the diastereoisomers as in the subsequent aromatisation of the cycloadducts these stereocenters are lost.

The following aromatisation can be achieved by oxidative extrusion of the bridging sulfoxy-unit, where phase transfer catalysed oxidation with $KMnO_4$ gives the best results (Scheme 4). On the other hand, when the oxidative cycloaddition reactions are run with an excess of *m*-CPBA, the aromatised compounds are obtained in one step (Scheme 4). At higher temperatures the cyano group undergoes a partial hydrolysis to the amide in this reaction.

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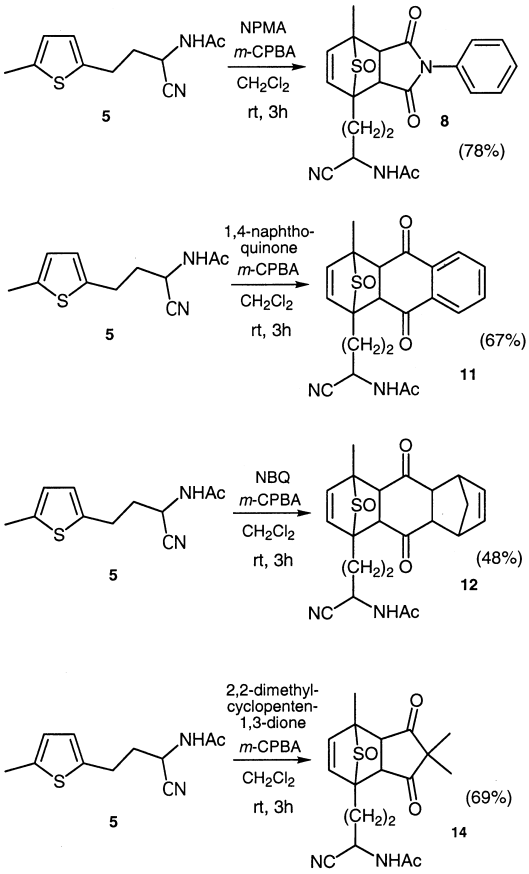
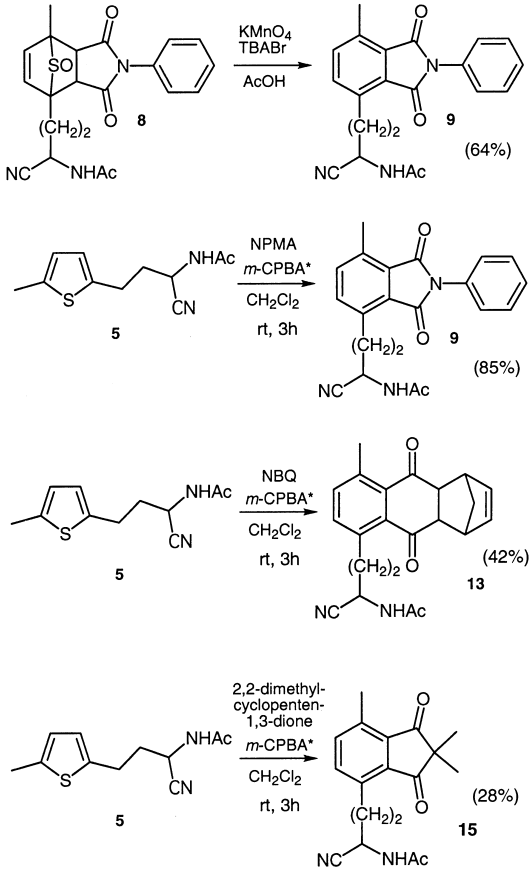


Scheme 3



Scheme 4

The cycloaddition of **5** with alkynes such as with dibenzoylacetylene directly yields aromatized compounds such as **17** (Scheme 5). As an example the conversion of these aromatised products has been performed with **17**, where **17** was treated with 2N aq. HCl to produce **20**·HCl. Refluxing **20**·HCl with propylene oxide provided the aminocarboxylic acid **20** itself (Scheme 5).

Techniques used: IR, ^{1}H NMR, ^{13}C NMR, MS, HRMS

Schemes: 6

References: 32

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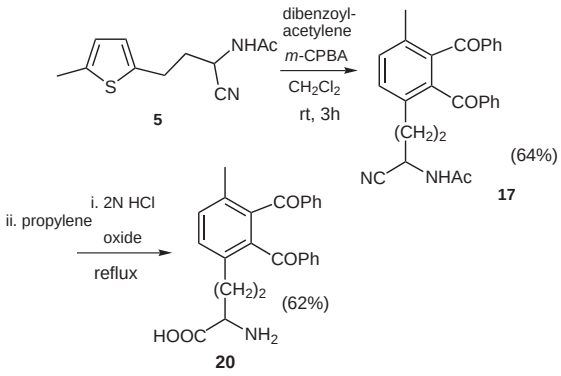

Scheme 5

References cited in this synopsis

1 For a typical recent review, see: M.L. Gelmi and D. Pocar, *Org. Prep. Proc. Int.*, 2003, **35**, 141.
4 L. Chen, J.W. Tilley, T.-N. Huang, D. Miklowski, R. Trilles, R.W. Guthrie, K. Luk, A. Hanglow, K. Rowan, V. Schwinge and B. Wolitzky, *Biol. Med. Chem. Lett.*, 2000, **10**, 725.
5 J. Meiwes, M. Schudok and G.C. Kretschmar, *Tetrahedron Asymmetry*, 1997, **8**, 527.
6 S.A. Fleming, *Tetrahedron*, 1995, **51**, 12479.
7 B. Kayser, J. Altman and W. Beck, *Tetrahedron*, 1997, **53**, 2475.
8 A.M. Naperstkow, J.B. Macaulay, M.J. Newlands and A.G. Fallis, *Tetrahedron Lett.*, 1989, **30**, 5077.
10 Y.Q. Li, T. Thiemann, T. Sawada and M. Tashiro, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2323.
11 T. Thiemann, Y.Q. Li, S. Mataka and M. Tashiro, *J. Chem. Res.* (*S*), 1995, 384; (*M*), 1995, 2364.
22 A.S. Cieplak, *J. Am. Chem. Soc.*, 1981, **103**, 4540.
23 For a review, see: A.S. Cieplak, *Chem. Rev.*, 1999, **9**, 1265.