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Diels-Alder Reactions of 2-Azadienes Derived From Cysteine Methyl Ester

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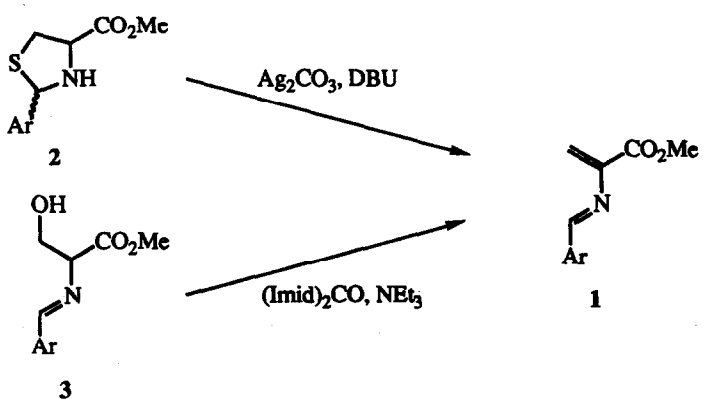
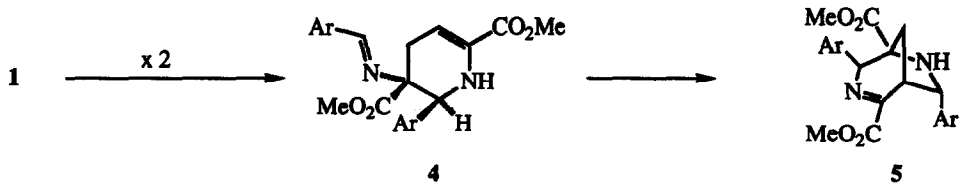
Abstract: The thiazolidines **2**, derived from L-cysteine methyl ester and aromatic aldehydes, react with silver carbonate and DBU to give methyl 2-(arylideneamino)acrylates **1**. These 2-azadienes undergo Diels-Alder reactions with both electron rich dienophiles and electron deficient dienophiles.

Oxazoles and 1,2,4-triazines are well known to act as 2-azadienes in the Diels-Alder reaction; their cycloaddition to alkenes provides an important method of synthesis of pyridines.[1] Acyclic 2-azadienes can similarly be used as precursors to dihydropyridines and tetrahydropyridines;[1] examples include species which are electron rich,[2] those which are electron deficient,[3] and those which are unactivated.[4]

In 1979 Öhler and Schmidt reported a method of preparation of the *N*-arylidenedehydroamino esters **1** by reaction of the thiazolidine esters **2** with silver carbonate and DBU.[5] These compounds were later prepared by Wulff and Böhnke by an alternative route, which involved the dehydration of Schiff bases **3** of serine methyl ester with *N,N'*-dicarbonylimidazole and triethylamine.[6] This procedure allowed the dehydroamino esters to be isolated and characterised. Subsequently Wulff and his co-workers have shown that these compounds undergo dimerisation by a stereoselective Diels-Alder reaction in which one molecule acts as the dienophile and another as a 2-azadiene. The dimers **4** can then cyclise to produce the bridged aminoesters **5**.[7]

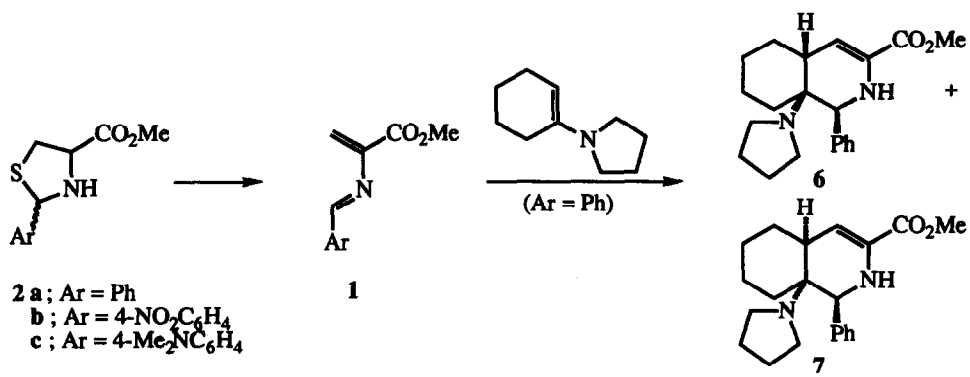




We have found that if the dehydroaminoesters **1** are generated in the presence of a suitable dienophile, cycloaddition to the dienophile can compete with this dimerisation process. We have used both the literature procedures for the generation of the dehydroaminoesters **1** and have found that a modification of the method of Öhler and Schmidt gives cycloadducts in better yields. Both electron rich and electron deficient dienophiles can be used in the reaction.

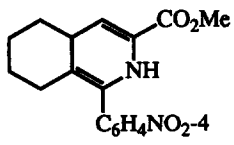
Thiazolidines **2**[8], prepared as described by Öhler and Schmidt, were dissolved in dry acetonitrile and the dienophile was added in excess. Silver carbonate was added in equimolar amount to the cooled solution, followed by DBU. The reaction mixtures were stirred overnight and the products were isolated by flash chromatography. Cycloadducts were, with a few exceptions, isolated in moderate to poor yield. In all cases cycloaddition was highly regioselective but not *endo–exo* stereoselective. It is apparent that the primary cycloadducts can undergo a variety of reactions, including prototropy, oxidation[9] and elimination, under the conditions used, and this results in mixtures of products in several of the reactions which we have examined.

Examples of the reactions are as follows. The thiazolidine **2a** reacted with 1-pyrrolidinocyclohexene to give the cycloadducts **6** (37%) and **7**[10] (20%). Compound **2a** with 1-pyrrolidinocyclopentene gave a single adduct (of structure analogous to **7**) in 35% yield. On the other hand a reaction of the thiazolidine **2b** with 1-pyrrolidinocyclohexene (carried out to determine whether a more electron deficient aryl substituent would improve the efficiency of the Diels-Alder reaction) gave two different types of adduct: an elimination product **8** (53%) and the tetrahydroisoquinoline **9** (20%) presumably derived from **8** by oxidation.[11]



No cycloadduct was obtained from a reaction carried out with compound **2a** in the presence of ethyl vinyl ether. With methyl vinyl ketone and several other electrophilic alkenes, however, cycloadducts were isolated in moderate to low yield. The reaction products obtained from **2a** and methyl vinyl ketone proved to be dependant upon the reaction conditions. Three products were identified from a reaction carried out as

described earlier. These were identified as compounds **10a** (20%), **11a** (5%) and **12** (51%).[12] The major product, **12**, must be derived from one or both of the primary cycloadducts by prototropy. A reaction carried out using silver carbonate on Celite (Fetizon's reagent) gave only compounds **10a** (27%) and **11a** (4%). The reaction with methyl vinyl ketone was also carried out with the intermediate **1** (Ar = Ph) generated from serine methyl ester by the method of Wulff and Böhnke; the only product isolated was the tetrahydropyridine **12** (17%). The more electron rich azadiene **1** (Ar = 4-$Me_2NC_6H_4$), derived from the thiazolidine **2c** and silver carbonate, reacted with methyl vinyl ketone to give a single product, the *cis* isomer **10b** (39%). On the other hand the only product isolated (7%) from **2a** and acrylonitrile was the *trans* isomer **11b**. Although all these reactions show the same regioselectivity it is difficult to draw any firm conclusions about the *endo–exo* selectivity of the initial reaction because of the easy prototropy in the adducts.



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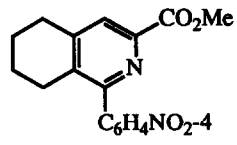

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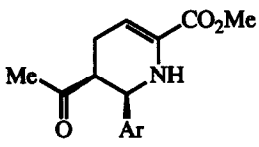
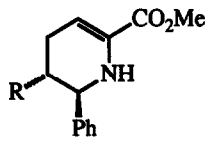
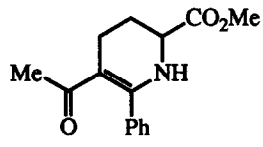


10 a ; Ar = Ph
b ; Ar = 4-$Me_2NC_6H_4$



11 a ; R = COMe
b ; R = CN



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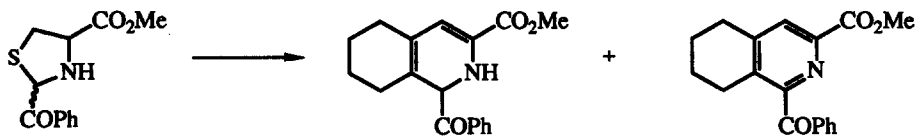
Cycloadducts were also isolated in low yield and characterised from reactions with methyl acrylate, diethyl fumarate and ethyl propiolate. The products were partially or fully oxidised: for example, diethyl fumarate gave 3,4-bis(ethoxycarbonyl)-6-methoxycarbonyl-2-phenylpyridine (15%). No adducts could be isolated from reactions with dimethyl acetylenedicarboxylate, dibenzoylacetylene and diethyl azodicarboxylate. An attempt to carry out an intramolecular cycloaddition to an unactivated double bond (using a thiazolidine derived from 2-allyloxybenzaldehyde) was also unsuccessful.

This chemistry is not limited to thiazolidines derived from aromatic aldehydes. Phenylglyoxal and cysteine methyl ester gave the thiazolidine **13**.[13] This compound reacts with silver carbonate in the presence of enamines in the same way as the thiazolidines **2**: for example, with pyrrolidinocyclohexene it gave compounds **14** (35%) and **15** (14%).



13 **14** **15**

1 Boger, D. L.; Weinreb, S. N. 'Hetero Diels-Alder Methodology in Organic Synthesis', Academic Press, San Diego, 1987.

2 Bayard, P.; Sainte, F.; Beaudegnies, R.; Ghosez, L. *Tetrahedron Lett.*, **1988**, *29*, 3799–3802, and references therein; Gouverneur, V.; Ghosez L.; *Tetrahedron Lett.*, **1991**, *32*, 5349–5352.

3 Barluenga, J.; Tomás, M.; Ballesteros, A.; Gotor, V. *J. Chem. Soc., Chem. Commun.*, **1987**, 1195–1196; Barluenga, J.; Tómas, M.; Ballasteros, A.; Gotor, V. *J. Chem. Soc., Chem. Commun.*, 1989, 267–269.

4 Barluenga, J.; Joglar, J.; González, F. J.; Fustero, S. *Synlett.*, **1990**, 129–138.

5 Öhler, E.; Schmidt, U. *Chem. Ber.*, **1979**, *112*, 107–115.

6 Wulff, G.; Böhnke, H. *Angew. Chem. Int. Ed. Engl.*, **1984**, *23*, 380–381; Wulff, G.; Böhnke, H.; Klinken, H. T. *Liebigs Ann. Chem.*, **1988**, 501–505. For another approach to compounds of this type see Tarzia, G.; Balsamini, C.; Spadoni, G.; Duranti, E. *Synthesis*, **1988**, 514–517.

7 Wulff, G.; Böhnke, H.; *Angew. Chem. Int. Ed. Engl.*, **1986**, *25*, 90–92; Wulff, G.; Lindner, H. G.; Böhnke, H.; Steigel, A.; Klinken, H. T. *Liebigs Ann. Chem.*, **1989**, 527–531; Wulff, G.; Klinken, H. T. *Tetrahedron*, **1992**, *48*, 5985–5990.

8 These compounds are formed as mixtures of diastereoisomers, as described in ref. 5. We were unable to separate the isomers by TLC or by column chromatography. There is no evidence from NMR for the presence of open chain (Schiff base) tautomers in reactions carried out with aromatic aldehydes but these tautomers could be detected in reactions with ketones.

9 Silver carbonate has been shown to be an oxidant for piperidines: Büchi, G.; Wüest, H. *J. Org. Chem.*, **1971**, *36*, 609–610.

10 Yields are for isolated compounds. **6**: m.p. 126–128 °C; δ (200 MHz, $CDCl_3$) 1.40–1.70 (14 H, m), 2.65–2.85 (2 H, m), 2.82–2.88 (1 H, m, 4a-H), 3.79 (3 H), 4.20 (1 H, d, *J* 2.4, 1-H), 4.67 (1 H, NH), 5.53 (1 H, d, *J* 2.4, 4-H) and 7.18–7.30 (5 H, m, Ar-H). **7**: m.p. 129–131 °C; δ 1.15–1.85 (12 H, m), 1.05–2.30 (2 H, m), 2.65–2.85 (2 H, m), 2.95–3.04 (1 H, m, 4a-H), 3.68 (3 H), 3.93 (1 H, NH), 4.54 (1 H, 1-H), 5.56 (1 H, 4-H), 7.25–7.35 (3 H, m, Ar-H) and 7.40–7.50 (2 H, m, Ar-H). (Relative stereochemistry requires confirmation by X-ray crystallography). These and other new compounds were characterised by elemental analysis and by MS.

11 **8**: m.p. 98–100 °C; δ 1.25–1.80 (6 H, m), 1.83–1.88 (1 H, m), 2.20–2.32 (1 H, m), 3.30–3.45 (1 H, m, 4a-H), 3.79 (3 H), 5.18 (1 H, NH), 5.45 (1 H, d, *J* 3.6, 4-H), 7.49 (2 H, d, *J* 8.8, Ar-H) and 8.23 (2 H, d, *J* 8.8, Ar-H). **9**: m.p. 161–162 °C; δ 1.70–2.00 (4 H, m), 2.67 (2 H, t, *J* 6.0), 2.94 (2 H, t, *J* 6.0), 3.98 (3 H), 7.68 (2 H, d, *J* 8.8, Ar-H), 7.93 (1 H, 4-H) and 8.31 (2 H, d, *J* 8.8, Ar-H).

12 **10**: m.p. 78–80 °C; δ 1.96 (3 H), 2.43 (2 H, approx. dd, *J* 7.0 and 4.4, 4-H), 3.05–3.15 (1 H, m, 5-H), 3.18 (3 H), 4.64 (1 H, NH), 4.72 (1 H, d, *J* 3.8, 6-H), 5.78 (1 H, t, *J* 4.4, 3-H) and 7.18–7.38 (5 H, m, Ar-H). **11**: oil; δ 1.71 (3 H), 2.22 (1 H, approx dt, *J* 18.8 and 5.3, 4-H), 2.48 (1 H, ddd, *J* 18.8, 9.7 and 3.6, 4-H), 2.86 (1 H, ddd, 5-H), 3.72 (3 H), 4.15 (1 H, d, *J* 8.5, 6-H), 4.25 (1 H, NH), 5.71 (1 H, dd, *J* 5.3 and 3.6, 3-H) and 7.22–7.30 (5 H, m, Ar-H). **12**: m.p. 136–137 °C; δ 1.56 (3 H), 1.65–1.85 (1 H, m, 3-H), 2.25–2.40 (2 H, m, 3-H and 4-H), 2.75–2.95 (1 H, m, 4-H), 3.80 (3 H), 3.98 (1 H, approx. dt, *J* 10.0 and approx. 2, 2-H), 4.77 (1 H, NH) and 7.35–7.45 (5 H, m, Ar-H); ν_{max} (KBr) 1749 (C=O of ester) and 1571 cm^{-1}.

13 The thiazolidine is again formed as a mixture of diastereoisomers but these can now be separated by column chromatography.

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