Pergamon

Tetrahedron Letters 41 (2000) 8699–8703

TETRAHEDRON LETTERS

α,β-Differentiated tandem diamination of cinnamic esters using *N*,*N*-dichloro-2-nitrobenzenesulfonamide and acetonitrile as the nitrogen sources

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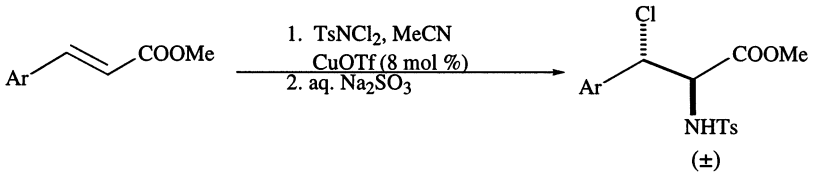
Received 24 April 2000; revised 5 September 2000; accepted 11 September 2000

Abstract

Tandem diamination of cinnamic esters provides a new approach to *anti* alkyl *N*α-(2-Ns), *N*β-Ac diaminophenylpropionates. The new reaction proceeds to completion within 3 hours at room temperature using *N*,*N*-dichloro-2-nitrobenzenesulfonamide (2-$NsNCl_2$) as the nitrogen source in acetonitrile, which is also involved in the reaction process. Seven diamine derivatives have been obtained with good yields and stereoselectivity.

Keywords: diamination; vicinal diamines; nitrobenzenesulfonamide; α,β-diamino acids.

Vicinal diamine derivatives are important building blocks in organic and medicinal chemistry.[1] The development of efficient synthetic approaches to this functionality in highly stereoselective fashions still remains challenging, especially when cinnamic esters, one of the most important olefinic classes,[2] are employed as the substrates. Recently, we developed a new vicinal aminohalogenation of cinnamic esters using *N*,*N*-dichloro-*p*-toluenesulfonamide ($TsNCl_2$) as the nitrogen and chlorine sources with transition metal compounds, $ZnCl_2$ and $Cu(OTf)_2$, as the catalysts in acetonitrile (Scheme 1).[3] In the continuing studies of this process, we attempted to



Scheme 1.

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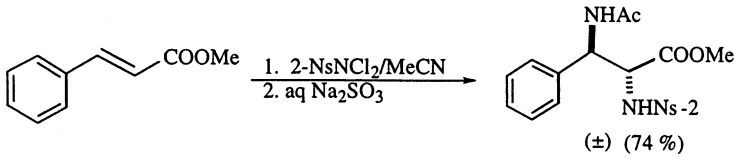
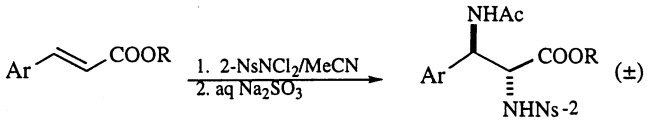
0040-4039/00/$ - see front matter
PII: S0040-4039(00)01579-3

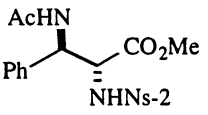
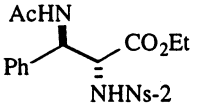
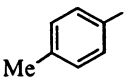
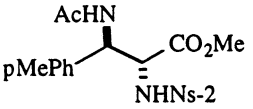
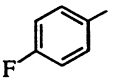
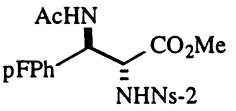
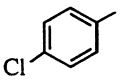
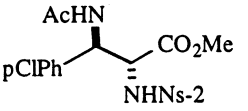
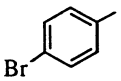
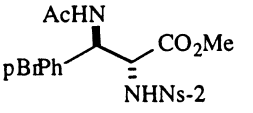
utilize the analogous nitrogen/halogen sources, such as 2-$NsNCl_2$, 4-$NsNCl_2$, 2,4-di-$NsNCl_2$, $RO(C{=}O)NCl_2$, to ensure easier deprotection under mild conditions. We found that the electrophilic nitrogen source, *N*,*N*-dichloro-nitrobenzenesulfonamide resulted in a novel diamination reaction, in which acetonitrile participated, to afford *anti* alkyl *N*α-(2-Ns),*N*β-Ac diaminophenylpropionates. In this communication we report the preliminary study of this new reaction, which is represented in Scheme 2 and the results summarized in Table 1.



Scheme 2.

Table 1
Results of the diamination of cinnamates[5]



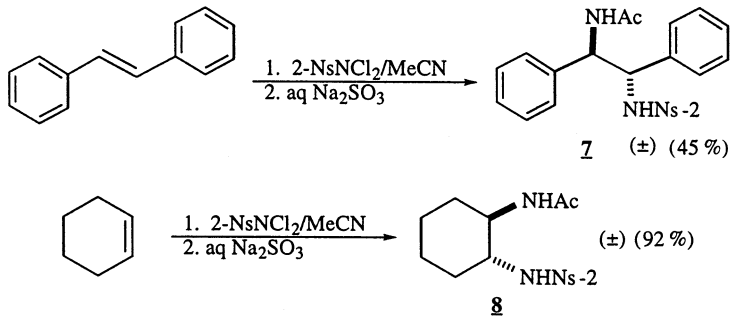
Ar	R		product[a]	yield (%)[b]
	Me	**1**		74
	Et	**2**		73
	Me	**3**		63
	Me	**4**		61
	Me	**5**		67
	Me	**6**		63

[a] The *anti*/*syn* selectivity for **4**, **5** and **6** was determined by ^{1}H-NMR as 2.1:1.0, 2.3:1.0 and 10:1.0, respectively. It is difficult to estimate *anti*/*syn* selectivity for **1-3** because of the complexity of crude ^{1}H-NMR. [b] Purified yields after flash column chromatography (EtOAc/Hexane/MeCN, 3/7/0.5, v/v/v).

The initial experiment was started under the known conditions[3] by replacing *N*,*N*-dichloro-*p*-toluenesulfonamide with *N*,*N*-dichloro-*p*-nitrobenzenesulfonamide (4-$NsNCl_2$) to react with methyl cinnamate. We anticipated that methyl *anti* 3-chloro-2-(*p*-nitrobenzenesulfonamido)-3-phenylpropionate would be produced in which the nitrobenzenesulfonyl protecting group can be readily cleaved by treating with PhSH and K_2CO_3 in DMF at room temperature.[4] Surprisingly, this reaction proceeded to completion in the absence of a catalyst [$ZnCl_2$ or $Cu(OTf)_2$] to give the same product mixture as that obtained when the catalyst was employed. Moreover, the major product is not a haloamine derivative but the α,β-diamino ester.

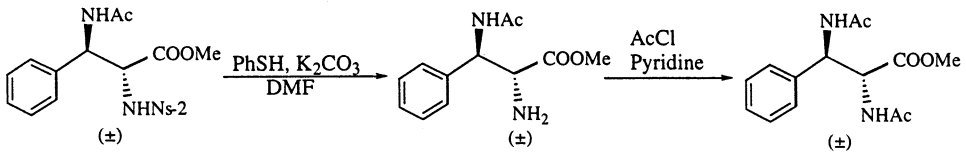
With these encouraging results, we then attempted to improve the yield as well as the stereoselectivity by replacing 4-$NsNCl_2$ with 2-$NsNCl_2$ and 2,4-di-$NsNCl_2$ as the nitrogen sources. We found that 2-$NsNCl_2$ can react with methyl cinnamate to afford alkyl *anti* *N*α-Ns, *N*β-Ac diaminophenylpropionates in greater efficiency than 4-$NsNCl_2$. However, the reaction of methyl cinnamate with 2,4-di-$NsNCl_2$ resulted in complex mixture with no improvement.

The reaction was readily carried out by stirring the acetonitrile solution of methyl cinnamate with *N*,*N*-dichloro-nitrobenzenesulfonamide at room temperature. Methyl cinnamate was consumed within 3 hours. The reaction can also proceed at 0°C to give similar results but at a slower rate. Good yields (61–74%) have been obtained for six examples we examined. Beside cinnamate substrates, normal olefins can also be employed for this reaction. The highest yield (92%) was obtained when cyclohexene was subjected to the reaction without the observation *syn* isomeric product. However, *trans*-stilbene gave a poor yield (45%) which is mainly due to the formation of haloamine side products (Scheme 3).



Scheme 3.

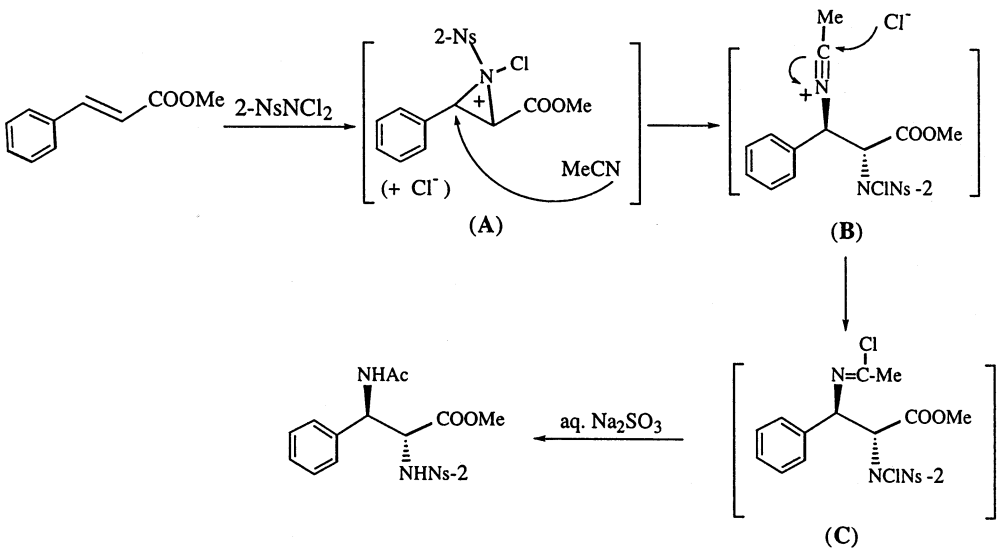
Regioselectivity of the product was determined by MS spectroscopic analysis in which two species, $[C_6H_5CHNHCOMe]^+$ and $[NsNHCHCO_2Me]^+$ were clearly identified. The stereochemical assignment was confirmed by the synthetic conversion of the product **1** in Table 1 to a known sample as illustrated in Scheme 4. During this conversion, the selective deprotection of the *N*α-Ns group was performed within 15 minutes under Fukuyama's condition.[4] The methyl



Scheme 4. Synthetic methods for structural determination

anti $N\alpha$-Ac, $N\beta$-Ac diaminophenylpropionate was obtained upon the treatment of the cleaved product with acetyl chloride in pyridine. Obviously, acetonitrile solvent is involved in the reaction process acting as the second nitrogen source. The $N\beta$-Ac functional group was generated upon quenching the reaction with aqueous Na_2SO_3.

This reaction is suggested to proceed through the formation of an unprecedented *N*-(2-nosyl),*N*-chloro aziridinium intermediate (**A**) at the first step (Scheme 5). The electronic deficiency of *N*,*N*-dichloro-nitrobenzenesulfonamide makes this new nitrogen source more reactive toward cinnamic esters than its *p*-toluenesulfonamide counterpart. Concurrently, this property makes the aziridinium intermediate (**A**) more electrophilic for reacting with acetonitrile via S_N2 mechanism which is responsible for the *anti* stereoselectivty. The regioselective outcome is due to the fact that the β-position of the aziridinium intermediate has more positive charge than the α-position because of the stabilization effect from the phenyl ring. This carbon–nitrogen bond formation is similar to the fashion of the Ritter reaction[6] in which nitrile reacts with normal carbocation intermediates generated from electrophilic addition of olefins or from dehydration of alcohols. The imino intermediate (**C**) is produced by the reaction between the nitrilium cation (**B**)[7] and Cl^-. Similar imino moieties can be found in olefin electrophilic addition reactions participated by acetonitrile.[8] The final stage of the present diamination involves the reduction of Cl-*N*α-(2-Ns) group to H-*N*α-(2-Ns) as well as the hydrolysis of N=C(Cl)Me moiety to NHAc group.



Scheme 5.

In conclusion, a tandem diamination of cinnamic esters has been developed by using *N*,*N*-dichloro-*o*-nitrobenzenesulfonamide (2-$NsNCl_2$) as the nitrogen source. The reaction can be conducted at room temperature without the need of inert atmosphere protection and provides a novel approach to methyl *anti* $N\alpha$-Ns, $N\beta$-Ac diaminophenylpropionate derivatives.

N-(2-nosyl),*N*-chloro aziridinium species generated in this process is a novel intermediate and could find more applications in organic synthesis by reacting with a variety of nucleophiles.

Acknowledgements

We would like to acknowledge the Robert A. Welch Foundation and the South Plains Foundation for supporting this work. We thank Mr. David W. Purkiss and Mr. Subramanian Karur for their assistance.

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5. The typical procedure is demonstrated by the diamination of methyl *trans*-cinnamate with *N*,*N*-dichloro-*o*-nitrobenzenesulfonamide (entry 1, Table 1). Into a dry vial is added methyl cinnamate (162 mg, 1.00 mmol) and freshly distilled acetonitrile (3.0 mL). *N*,*N*-Dichloro-*o*-nitrobenzenesulfonamide (406 mg, 1.50 mmol) is then added into the above homogeneous solution. The reaction vial is capped and immersed in a bath at room temperature. The resulting solution in the capped vial was stirred for 3 h. TLC monitoring shows the disappearance of methyl *trans*-cinnamate. The reaction was finally quenched by the addition of saturated aqueous Na_2SO_3 solution (3 mL). The phases were separated, and the aqueous phase was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated to dryness. Purification by flash chromatography (EtOAc/hexane/MeCN 3/7/0.5, v/v/v) provided methyl *anti* *N*α-Ns, *N*β-Ac diaminophenylpropionate **1** (312 mg, 74% yield) as colorless oil.
   ^{1}H NMR data, Table 1 (300 MHz, $CDCl_3$). Compound **1**: δ 8.05 (m, 1H), 7.60 (m, 3 H), 7.19 (m, 5H), 5.49 (dd, J=4.28, 7.88, 1H), 4.62 (d, J=4.28, 1H), 3.46 (s, 3H), 2.60 (s, 3H). **2** δ 8.02–8.07 (m, 1H), 7.55–7.62 (m, 3H), 7.40 (d, 1H, NH), 7.16–7.24 (m, 5H), 5.49 (dd, J=4.27, 7.83, 1H), 4.59 (d, J=4.23, 1H), 4.09 (q, J=7.09, 2H), 2.60 (s, 3H), 1.10 (t, J=7.18, 1H). **3**: δ 8.10–7.00 (m, 8H), 5.46 (dd, J=4.32, 7.88, 1H), 4.62 (d, J=4.32, 1H), 3.64 (s, 3H), 2.58 (s, 3H), 2.04 (s, 3H). **4**: δ 8.30–6.80 (m, 8H), 5.45 (dd, J=4.31, 7.59, 1H), 4.58 (d, J=4.31, 1H), 3.66 (s, 3H), 2.59 (s, 3H). **5**: δ 8.30–7.00 (m, 8H), 5.42 (dd, J=4.29, 7.41, 1H), 5.16 (d, J=4.09, 1H), 4.56 (d, J=4.29, 1H), 3.67 (s, 3H), 2.59 (s, 3H). **6**: δ 8.04 (m, 1H), 7.62 (m, 3H), 7.26 (m, 2H), 7.02 (m, 2H), 5.39 (dd, J=4.30, 7.32, 1H), 4.55 (d, J=4.30, 1H), 3.66 (s, 3H), 2.59 (s, 3H). **7**: δ 8.20–8.26 (m, 1H), 7.63–7.74 (m, 3H), 6.29 (d, J=7.72, 1H, NH), 3.84–3.91 (m, 2H), 2.48 (s, 3H), 2.15–2.26 (m, 2H), 1.15–1.79 (m, 6H). **8**: δ 7.94–7.97 (m, 1H), 7.55–7.60 (m, 3H), 7.00–7.32 (m, 10 H), 6.8 (d, J=7.33, 1H), 5.40 (d, J=8.13, 1H), 5.16 (d, J=7.33, 1H), 2.52 (s, 3H).
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