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A novel regioselective method for aminostilbene preparation—the role of sodium azide

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ABSTRACT

The reaction between a derivative of 2,4-dinitrostilbene and sodium azide gave consistently 2-amino-4-nitrostilbenes as the sole products instead of the expected azidonitrostilbene. Based on this finding, we present a one-step preparative method for selective transformation of the *ortho*-NO_2 group in (*E*)-2,4-dinitrostilbenes into an *ortho*-NH_2 group to give (*E*)-2-amino-4-nitrostilbenes.

The chemistry and photochemistry of stilbenes have been investigated extensively.[1–3] Stilbene derivatives are usually thermally and chemically stable and possess absorption and fluorescence properties that can easily be monitored by relevant optical techniques. They play an increasingly prominent role in the area of photophysical, photochemical, biophysical and biomedical investigations. Preclinical research on cells, organs and animals using stilbenes has attracted significant attention as a necessary step for further clinical investigation and the invention of new drugs. Data on anticancer and other chemopreventive activities of resveratrol [RES, (*E*)-3,5,4′-trihydroxystilbene] and other stilbenes with a methoxy, nitro or amine group have been summarized.[4] Stilbene derivatives such as CA1 and the corresponding nitrogen analogue, AVE8062, along with the diphenol phosphate prodrug CA1P (also known as Oxi4503), CA4P (Fig. 1) and the corresponding nitrogen analogue, belong to the group of vascular-disrupting agents (VDAs) which have been subjected to clinical trials in humans.[5–11]

Due to the widespread use and importance of stilbenes, new, more selective and rapid methods for their synthesis are required. In continuation of our studies on stilbenes, we found, to our surprise, that the reaction between a derivative of 2,4-dinitrostilbene **1**–**5** and sodium azide always gave the corresponding 2-amino-4-nitrostilbene **6**–**10** as the sole product instead of the expected azidonitrostilbene[12] (Scheme 1). The conversion of a nitro group into an amine usually proceeds in the presence of a metal (Sn, Zn) and acids, but when using sodium azide, the product of substitution is obtained. Several reactions of azides in which the desired products[13–16] were not obtained, have been reported. In the first case, Sajiki and co-workers[13] reported that the cross-coupling reaction between ethyl 4-bromobenzoate and trimethylsilyl azide in the presence of Cu(I) catalysts and triphenylphosphine gave ethyl 4-aminobenzoate as the product instead of the expected ethyl 4-azidobenzoate. Two further articles describing copper-mediated aminations of aryl halides utilizing azides as the amine source have appeared.[14,15] However, the mechanism of the redox process was not disclosed. Kolarovič et al.[16] hypothesized that the strongly electron-withdrawing nitro group (with 1-iodo-4-nitrobenzene as the substrate in the reaction) made 1-azido-4-nitrobenzene (formed in situ) prone to reduction, and that water served as a hydrogen donor for the transformation into 4-nitroaniline.

Optimization of our reaction conditions for this unexpected transformation revealed the following: (1) sodium azide was required as without this reagent no product was observed, (2) 120 °C and DMF or DMSO was the best combination of temperature and solvent, (3) the reaction proceeded in air or under an argon atmosphere. The reaction was regiospecific with only the *ortho*-NO_2 group replaced. We obtained two known (**6** and **7**)[17,18] and three new (**8**–**10**) stilbenes using this method (Table 1).

We undertook experiments to investigate the mechanism of this reaction. Shevelev and co-workers[12] demonstrated that the *ortho*-NO_2 group in (*E*)-2,4,6-trinitrostilbenes was replaced regioselectively when exposed to an azide such as NaN_3 at ambient temperature.

We hypothesized initially that in compounds **1**–**5** the *ortho*-NO_2 group might also be replaced in the reaction with NaN_3. Unfortunately, despite running the reaction for 13 h at ambient temperature, the expected product was not observed. After increasing the temperature to 120 °C, we obtained products **6**–**10**. Complete ^{1}H

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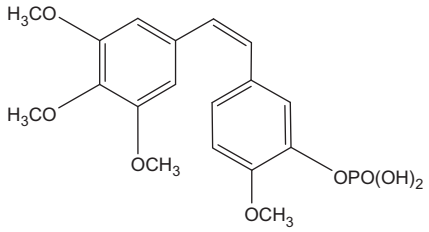


CA4P

Figure 1. The structure of **CA4P**.

and ^{13}C NMR spectroscopic data of all the products are shown in Tables 2 and 3 (see Supplementary data). The ^{1}H and ^{13}C NMR resonances were assigned unequivocally based on the combined information from 1D to 2D NMR (gCOSY, gHSQC and gHMBC) experiments. Coupling constants (^{1}H–^{1}H) were measured directly from resolution-enhanced 1D spectra and confirmed, when necessary, by homo-decoupling. gHSQC and gHMBC analysis allowed the assignment of the stilbene regiochemistry (Fig. 2), determination of the H-3, H-5, H-6 resonances and the assignment of important correlations (all of which occurred in all the stilbenes). The following correlations were observed for product **8**: protons of the amine group (4.09 ppm) with C-1 (129.47 ppm) and C-3 (110.50 ppm); C-2 (144.50 ppm) with H-3 (7.56 ppm), Hα 7.07 ppm and H-6 (7.49 ppm); H-3 (7.56 ppm) with C-1 (129.47 ppm), C-2 (144.50 ppm), C-4 (147.89 ppm) and C-5 (113.91 ppm).

Only in the case of substrate **2** did we observe the intermediate azide product **7a** (Fig. 3), which after about 1 h gradually disappeared with simultaneous formation of the final product **7**. NMR, IR and MS analysis of this intermediate showed the presence of an azide group at position 2 (see Tables 2 and 3 in the Supplementary data). However, we still did not know what the source of the hydrogen was for the transformation of the nitro compounds into 2-amino-4-nitrostilbenes in these reactions. We observed a signal that originated from the hydrogen of the amine group in the ^{1}H NMR spectrum. Having investigated the source of the hydrogen donor, we examined the reaction of **6** in DMSO-d_6. In the proton spectrum, we did not observe the hydrogens of the amine group. However, the ^{2}H NMR analysis displayed the deuterium in the amine group. Moreover pure azidostilbene **7a** was heated at 120 °C for 12 h in DMF (without using NaN_3) to afford product **7**. Thus, we concluded that the source of the hydrogen was in the

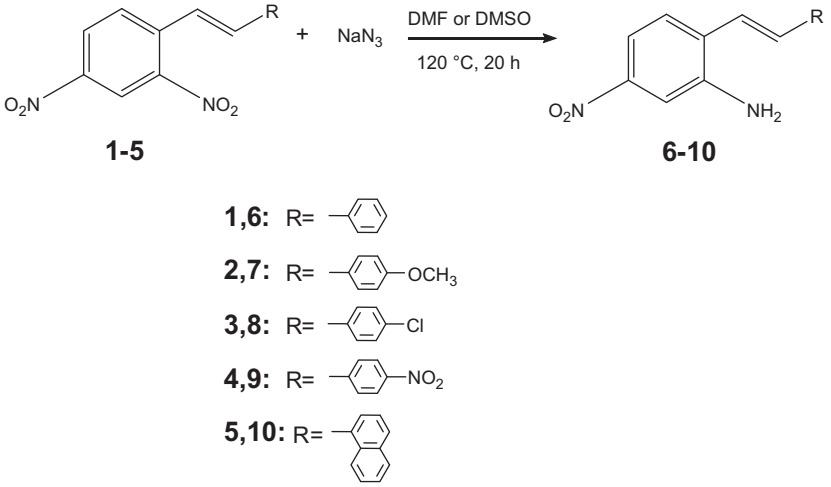
Table 1
Optimization of the reaction conditions for the transformation of 2,4-dinitrostilbene derivatives **1**–**5** into products **6**–**10**

Entry	Substrate	Product	Time (h)	Yield[a,b] (%)
1	**1**	**6**	8	85
2	**2**	**7**	15	80
3	**3**	**8**	20	85
4	**4**	**9**	20	89
5	**5**	**10**	20	75

[a] Isolated yield.
[b] DMF was used as the solvent; temperature = 120 °C.

reaction solution. Moreover, when the experiment was conducted in dry DMSO the products were still present, but in lower yields. These experiments indicate that water probably serves as the hydrogen donor in these processes. Furthermore, it is also not clear why only the nitro group at position 2 undergoes this transformation. It is known[19] that the nitro groups in 2-methyl-1,3,5-trinitrobenzene (TNT) are non-equivalent. Thus, the *para*-nitro group is coplanar with the benzene ring, whereas the two *ortho*-nitro groups are rotated around the C–N axis by ~40° and ~20° with respect to the benzene ring, due to the steric effect of the methyl group. This substantial non-coplanarity of the nitro group favours, in the case of the *ortho*-nitro group in TNT, the necessary change in hybridization of the *ipso*-C atom from sp^2 to sp^3 upon formation of the *ipso*-σ-complex, because rotation of the nitro group decreases its degree of conjugation with the aromatic ring. In order to study the positioning of the nitro groups, the optimum structure of **2** using the DFT B3LYP/6-311++G(2d,p) method was calculated. It appeared that as in TNT the *ortho*-nitro group of **2** was rotated around the C–N axis by ~32.5° and ~32.8°, and that the *para*-nitro group was coplanar with respect to the benzene ring. We hypothesize that the strong electron-withdrawing nitro group at position 4 in compounds **1**–**5** makes the nitro group at position 2 prone to substitution by the azide group and, as a result, vulnerable to reduction.

In conclusion, we have demonstrated that sodium azide reacts regiospecifically with only one of the two nitro groups among a variety of dinitrostilbenes, without the need for a catalyst, in DMF or DMSO at 120 °C to give 2-amino-4-nitrostilbenes as the sole products in satisfactory yields. This process can be regarded as a one-step preparative method for selective transformation of the *ortho*-NO_2 group in (*E*)-2,4-dinitrostilbenes into an *ortho*-NH_2 group to give (*E*)-2-amino-4-nitrostilbenes. On the basis of our investigations, we hypothesize that the strongly



Scheme 1. The unanticipated formation of aminostilbenes **6**–**10** from nitrostilbenes **1**–**5** under azidation conditions.

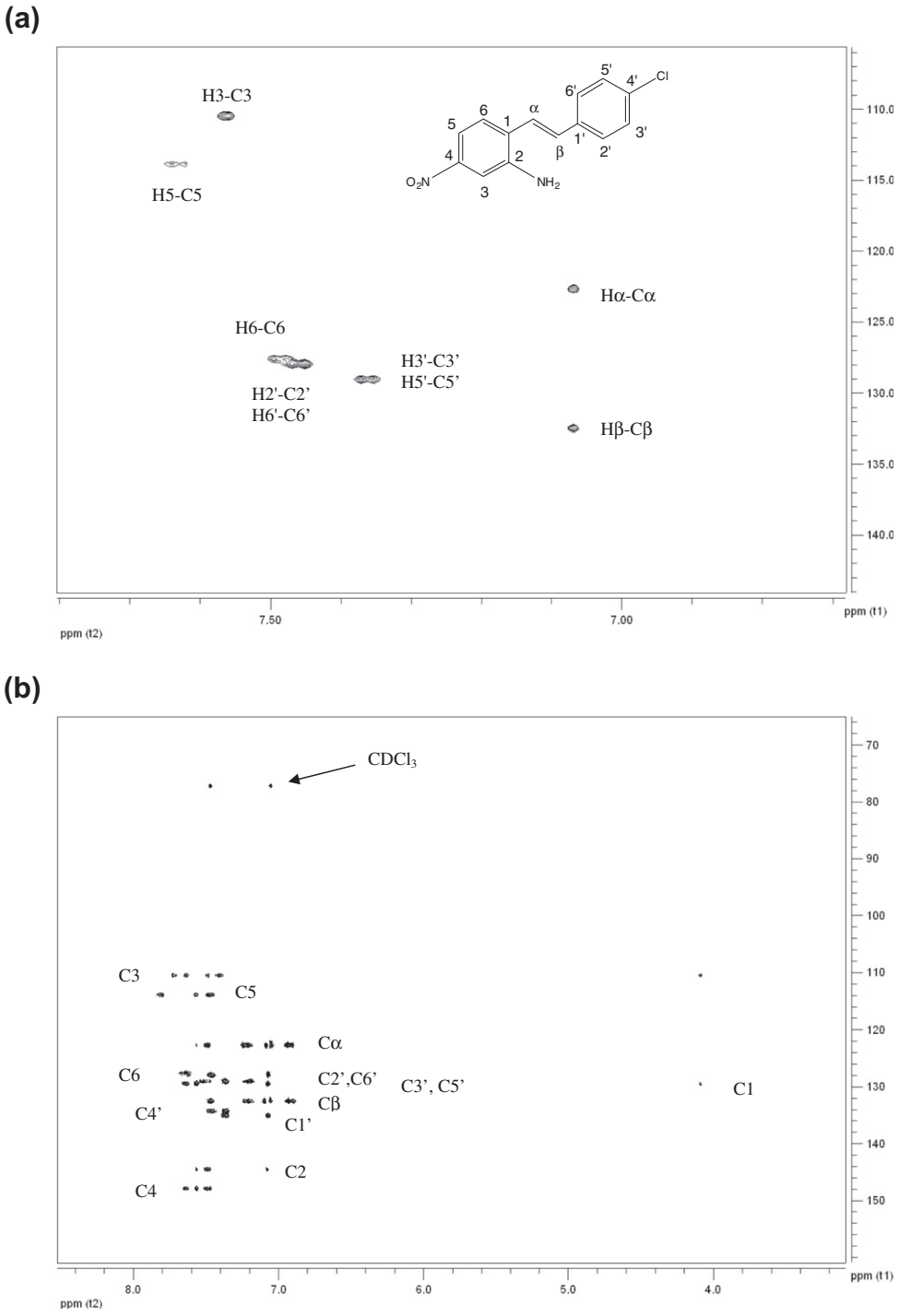


Figure 2. g-HSQC (a) and gHMBC (b) spectra of product **8**. The signals due to $CDCl_3$ at 77.0 ppm (^{13}C) and 7.26 ppm (^{1}H) were used as internal reference standards.

electron-withdrawing nitro group at position 4 in the substrates makes the nitro group at position 2 more prone to substitution by the azide group and subsequently to reduction into an amine group.

General procedure for the reductive amination of dinitrostilbenes with NaN_3 (Table 1)

2,4-Dinitrostilbene (1.70 mmol), and NaN_3 (190 mg, 2.95 mmol) in DMF (15 ml), were sequentially added to a three-necked flask (25 mL) fitted with a condenser. The mixture was stirred at 120 °C for 20 h and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (toluene → toluene: MeOH, 4:1).

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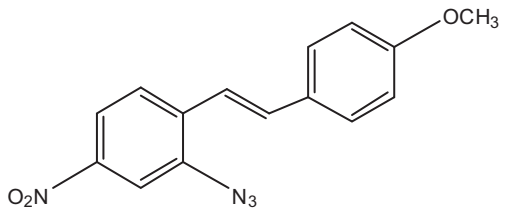

7a

Figure 3. The structure of **7a**.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.09.066.

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