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A CAN-Induced Cyclodimerization−Ritter Trapping Strategy for the One-Pot Synthesis of 1-Amino-4-aryltetralins from Styrenes[†]

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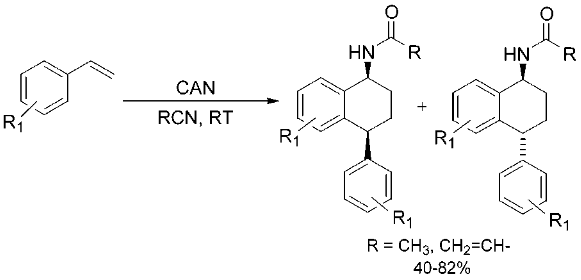
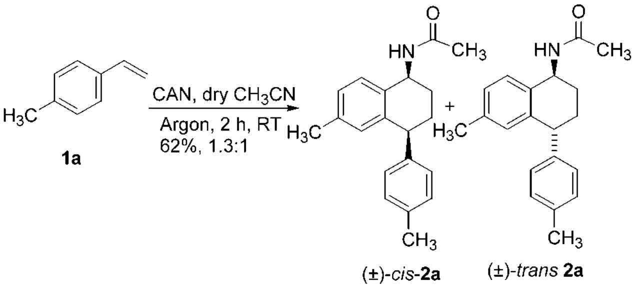
ABSTRACT



A facile one-pot synthesis of 1-amino-4-aryl-tetralin derivatives by the CAN-induced cyclodimerization of various styrenes in acetonitrile and acrylonitrile is described.

Ever since the pioneering work of Heiba and Dessau on cerium(IV) ammonium nitrate (CAN)-mediated carbon−carbon bond forming reactions there has been a number of studies in this area.[1] Our own investigations have uncovered some novel reactions including a dimerization of alkoxystyrenes mediated by CAN.[2] Intrigued by the possibility that an α-aminotetralin derivative may be formed by the cyclodimerization of styrenes if the reaction takes place in an environment conducive for the termination of the reaction by the Ritter trapping of the cationic intermediate, we exposed an acetonitrile solution of 4-methylstyrene **1a** to CAN in an argon atmosphere. In the event, a facile reaction occurred and the α-acetamido tetralins *cis*-**2a** and *trans*-**2a** were obtained (Scheme 1).

Scheme 1



It is noteworthy that α-aminotetralin derivatives manifest a number of important and therapeutically useful biological

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[†] This paper is dedicated with respect and affection to Professor Gilbert Stork, a legend in his own time, for the gift of chemistry he has given to hundreds of students during the past six decades.

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(1) (a) Heiba, E. I.; Dessau, R. M. *J. Am. Chem. Soc.* **1971**, *93*, 524. (b) Baciocchi, E.; Civatarесse, G.; Ruzziconi, R. *Tetrahedron Lett.* **1987**, *28*, 5357. (c) Nair, V.; Mathew, J.; Prabhakaran, J. *Chem. Soc. Rev.* **1997**, 127.

(2) (a) Nair, V.; Mathew, J.; Kanakamma, P. P.; Panicker, S. B.; Zeena, S.; Sheeba, V.; Eigendorf, G. K. *Tetrahedron Lett.* **1997**, *38*, 2191. (b) Nair, V.; Sheeba, V.; Panicker, S. B.; George, T. G.; Rajan, R.; Balagopal, L.; Vairamani, M.; Prabhakar, S. *Tetrahedron* **2000**, *56*, 2461.

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activities; some of them are potent CNS stimulants and others are antibiotics, immunomodulators, and antitumor agents.[3] Special mention may be made of the top selling antidepressant sertraline **3** (Figure 1).[4]

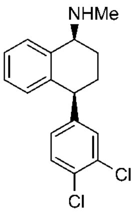

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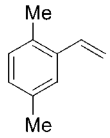
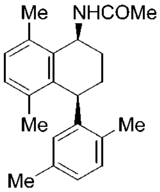
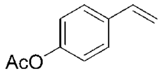
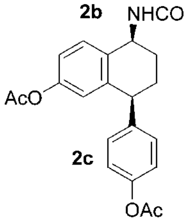
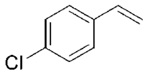
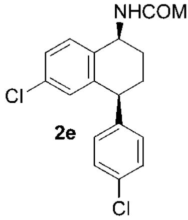
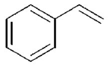
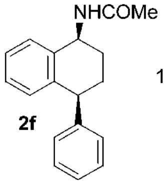
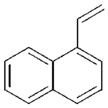
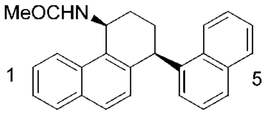
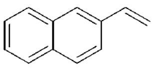
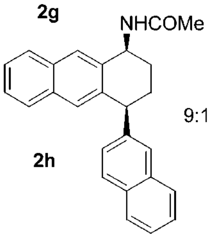
Figure 1. Sertraline.

In view of the potent biological activities of such α-aminotetralin derivatives by virtue of their structural similarity to sertraline, the mechanistic implication of the reaction, and the facility with which *cis*-**2a** and *trans*-**2a** are formed, it was obligatory for us to investigate the reaction in some detail.[5] Our preliminary results are presented here.

As already mentioned, in a pilot experiment, 4-methylstyrene on treatment with CAN in acetonitrile in a totally oxygen-free atmosphere afforded the α-acetamido tetralins *cis*-**2a** and *trans*-**2a** in 62% yield as diastereomers in the ratio 1.3:1 (Scheme 1). The α-acetamido tetralin *cis*-**2a** was characterized on the basis of spectroscopic data. In the ^{1}H NMR spectrum, the methyl group of the amide moiety resonated as a singlet at δ 2.02 while the two methyl groups on the aromatic rings resonated as two singlets at δ 2.19 and 2.34. The doubly benzylic proton was seen as a multiplet at δ 3.97−3.99 (for *trans*-**2a** this proton was seen in the range δ 4.03−4.06). The benzylic proton attached to nitrogen resonated as a multiplet at δ 5.13−5.15 (for *trans*-**2a** this proton resonated at δ 5.25−5.27). The NH proton resonated at δ 5.84, supporting the IR absorption at 3301 cm^{-1}. The ^{13}C signal for the amide carbonyl was seen at δ 168.99. Finally, the configuration of the major diastereomer was ascertained to be *cis* by single-crystal X-ray analysis (see Supporting Information).

Analogous results were obtained with a number of other styrenes, and the results are summarized in Table 1.

Table 1. Dimerization of Various Styrenes To Afford α-Acetamido Tetralin Derivatives

entry	styrene	time (h)	product[a]	cis/trans ratio[b]	yield(%)[c]
1	 **1b**	2	 **2b**	5:1	60
2	 **1c**	3	 **2c**	1.4;1	58
3	 **1e**	12	 **2e**	5:2	42
4	 **1f**	12	 **2f**	1.2:1	40
5	 **1g**	1	 **2g**	5:2	82
6	 **1h**	1	 **2h**	9:1	80

[a] Structure of the major isomer is shown. [b] Determined by HPLC analysis [c] Combined isolated yield of both isomers.

A mechanistic rationale for the formation of the α-acetamido tetralins is presented in Scheme 2. The styrene **1** in the presence of Ce(IV) undergoes oxidative electron transfer to afford the radical cation **I**, which in turn would add to another styrene molecule to generate a distonic radical cation **II**. This 1,4 radical cation undergoes 1,6 cyclization to give a substituted hexatriene radical cation **III**, which on losing a proton yields the radical intermediate **IV**.[6,7] The radical intermediate **IV** undergoes oxidation to a cation **V**, which

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(3) Lautens, M.; Rovis, T. *Tetrahedron* **1999**, *55*, 8967 and references therein.

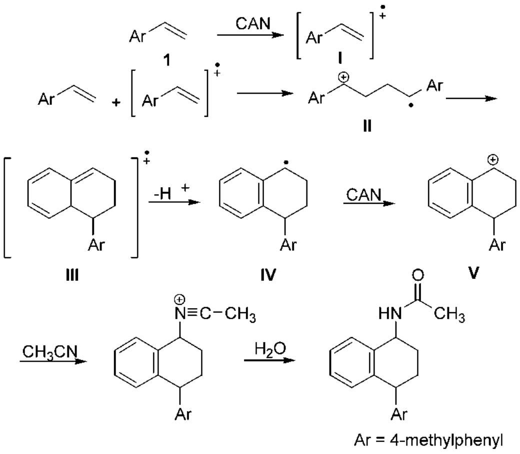
(4) (a) Welch, W. M.; Kraska, A. R.; Sarges, R.; Koe, B. K. *J. Med. Chem.* **1984**, *27*, 1508. (b) U.S. Patent 5,442,116, 1995. (c) Koe, B. K.; Weisman, A.; Welch, W. M.; Broune, R. G. *J. Pharmacol. Exp. Ther.* **1983**, *226*, 686. (d) William, M.; Quallich, G. *Chem. Ind. (London)* **1990**, *10*, 315. (e) Corey, E. J.; Gant, T. G. *Tetrahedron Lett.* **1994**, *35*, 5373. (f) Chen, C.; Reamer, R. A. *Org. Lett.* **1999**, *1*, 293. (g) Davies, H. M. L.; Stafford, D. G.; Hansen, T. *Org. Lett.* **1999**, *1*, 233.

(5) It may be mentioned that Baciocchi et al. have reported the formation of dinitrates from styrenes when the latter were treated with CAN in acetonitrile under photochemical or thermal conditions, the yields being quantitative in the latter case (Baciocchi, E.; Rol, C.; Giacco, D.; Murgia, S. M.; Sebastiani, G. V. *Tetrahedron* **1988**, *44*, 6651. Baciocchi, E.; Rol, C.; Sebastiani, G. V.; Zampini, A. *J. Chem. Soc., Chem. Commun.* **1982**, 1045).

(6) Bauld, N. L. *Tetrahedron* **1989**, *45*, 5307.

(7) Schepp, N. P.; Johnston, L. J. *J. Am. Chem. Soc.* **1996**, *118*, 2872.

Scheme 2

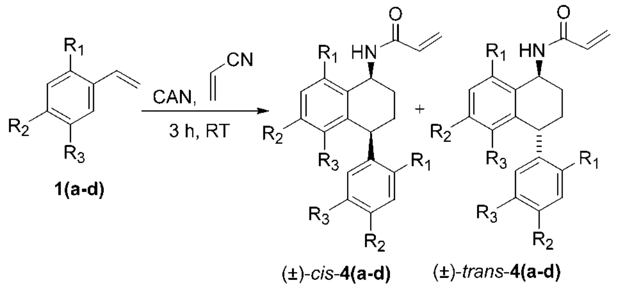


subsequently gets trapped by the solvent acetonitrile in a manner analogous to the Ritter reaction.[8,9]

Interestingly, when styrenes **1a−d** were treated with CAN employing acrylonitrile as the reaction medium, the corresponding α-acrylamido tetralin derivatives *cis*-**4a−d** and *trans*-**4a−d** were obtained (Scheme 3).

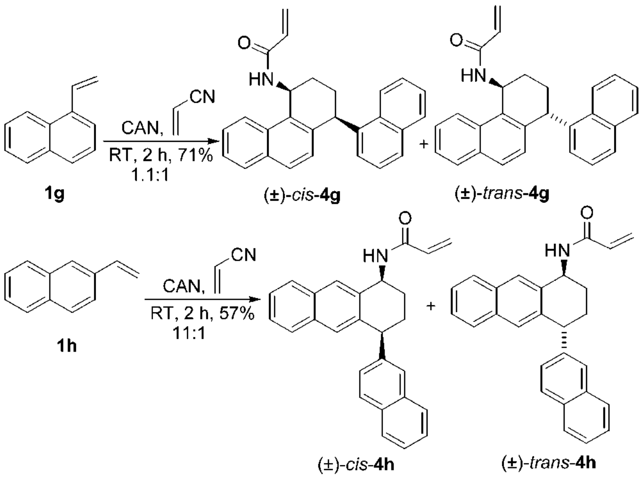
Vinyl naphthalenes **1g** and **1h** also afforded the corresponding α-acrylamido tetralin derivatives under the above conditions (Scheme 4).

Scheme 3



1a) $R_1 = H$, $R_2 = CH_3$, $R_3 = H$ (52%) *cis/trans*-1.3:1
1b) $R_1 = CH_3$, $R_2 = H$, $R_3 = CH_3$ (64%) *cis/trans*-7:1
1c) $R_1 = H$, $R_2 = OAc$, $R_3 = H$ (54%) *cis/trans*-1.3:1
1d) $R_1 = CH_3$, $R_2 = CH_3$, $R_3 = H$ (72%) *cis/trans*-1.2:1

Scheme 4



In conclusion, we have devised a novel and expeditious one-pot synthesis of α-aminotetralin derivatives that bear close resemblance to potent therapeutic agents. Further work to unravel the reaction mechanism, to expand the scope of the reaction, and to devise asymmetric synthesis are in progress; the results will be reported in due course.

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Supporting Information Available: General experimental procedures, IR, ^{1}H NMR, and ^{13}C NMR data for all compounds and single-crystal X-ray structure for *cis*-**2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[8] (a) Ritter, J. J.; Minieri, P. P. *J. Am. Chem. Soc.* **1948**, *70*, 4045. (b) Krimen, L. I.; Cota, D. J. *Org. React.* **1969**, *17*, 213. (c) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 6, 1.9, p 261.

[9] The oxidative ligand transfer leading to the formation of a benzylic nitrate and its intermediacy may also be considered as a possibility; this insight was provided by a referee.