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Study on the scope of *tert*-amino effect: new extensions of type 2 reactions to bridged biaryls†

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Thermal isomerization of aminomethyl- or oxygen-bridged biphenyl systems possessing dicyanovinyl and *sec*-amino groups in *ortho*- and *ortho*′-positions was investigated. Both systems underwent cyclization via *tert*-amino effect. Thus, 2-(2-{[2-(*sec*-amino)benzyl]-*N*-methylamino}benzylidene)malononitriles gave tetrahydroquinolines, whereas a 2-[2-(*sec*-amino)phenoxy]benzylidenemalononitrile isomerized to dibenzoxazonine derivative. The ring closure reaction was studied by differential scanning calorimetry measurements. Copyright © 2012 John Wiley & Sons, Ltd.

Keywords: *tert*-amino effect; isomerization; hydrogen migration; tetrahydroquinoline; oxazonine; dibenzoxazonine; differential scanning calorimetry

INTRODUCTION

The term "*t*-(*tert*)-amino effect" was introduced by Meth-Cohn and Suschitzky for isomerization reactions of *ortho*-substituted *tert*-anilines with ring closure to fused aza-ring systems.[1] Several subtypes of *tert*-amino effect have been distinguished, depending on the way of cyclizations and type of the ring formed.[2,3] One version of type 2 reactions, isomerization of *ortho*-vinyl-*tert*-anilines or their heterocyclic analogs to obtain benzo- or heteroring-fused tetrahydropyridines, has attracted much attention because of its predictable substituent effects as well as regio- and stereoisomeric aspects of the isomerization. In these reactions, a two-step mechanism has been postulated: (i) a rate-limiting hydrogen migration (with a sigmatropic [1,5] rearrangement or hydride transfer) to form a dipolar intermediate and (ii) ring closure of the intermediate with a C–C bond formation (Fig. 1).[3–7]

The first step might often require, particularly for isomerizations of π-deficient heterocyclic *tert*-amines, high temperatures and/or longer reaction times. To overcome the limitation of harsh conditions led us to apply microwave-assisted chemistry; in fact, our efforts have not only led to improved yields but also opened new ways to the syntheses of otherwise hardly accessible polycyclic ring systems.[8,9]

Further recent examples of type 2 *tert*-amino effect, including syntheses of pyrazolinoquinolizines and 1,4-oxazinopyrazolines,[10] 1,2-fused 5*H*-chromeno[4,3-*b*]pyridin-5-ones and 6*H*-benzo[*h*][1,6]naphthyridin-5-ones,[11] naphthalenes,[12] α-carbolines,[13] and spirocyclic 1,2,3,4-tetrahydroquinolines,[14] also demonstrate the versatility of such reactions.

It has more recently been reported that a Lewis acid ($Gd(OTf)_3$ operated optimal) might efficiently catalyze type 2 cyclization of alkylidene malonates,[15] although the scope of catalysis seems to be limited to ester group in the vinyl moiety. As an attractive feature of this approach, it could be mentioned that some degree of enantioselectivity could be achieved with enantiomers of chiral metal complexes or phosphoric acid.[16,17]

A mechanistically closely related "hydride transfer initiated cyclization"/"C–H bond functionalization" reaction was employed for the synthesis of dihydrobenzopyrans from the corresponding *ortho*-vinylaryl alkyl ethers with Lewis acid ($Sc(OTf)_3$ or $SnCl_4$)

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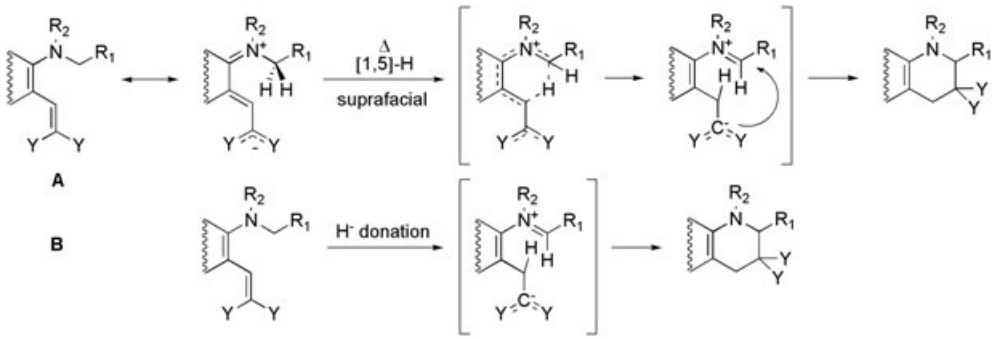


Figure 1. *tert*-Amino effect type 2 cyclizations

catalysis,[18,19] whereas the C-version of cyclizations via "hydride shift mediated C–H bond functionalization" was applied for the synthesis of 3-aryltetralines.[20]

In our extensive studies on kinetics, thermodynamics, regio- and stereochemistry as well as scope and limitations of the *tert*-amino effect, while recognizing important features of the mechanism, new extensions to biaryls and fused bicyclic systems incorporating the interacting amino and vinyl groups in the two *ortho* or *ortho* and *peri* positions, respectively, have been developed to provide easy accesses to medium or macrocyclic rings (Fig. 2).[21–23]

Interestingly enough, in the biaryl and naphthalene series, novel zwitterionic phenantridium or benzo[*d*,*e*]quinolinium systems could also be obtained through a Michael type addition (Fig. 3). Our X-ray data of the vinyl compounds revealed a nonbonding interaction between the tertiary nitrogen and the α-vinylic carbon, which might also play a role in the reaction.

As a continuation of these studies, our aim was to investigate cyclization reactions of nondirectly connected biaryl systems; in the rate-limiting step of the rearrangement reaction of such compounds via *tert*-amino effect, a sigmatropic hydrogen migration *a priori* could be excluded (Fig. 1: pathway A); instead, a direct hydride transfer could only take place (Fig. 1: pathway B). Although formation of benzazepine derivatives via "homologous *tert*-amino effect" was reported,[24] further extensions have not been explored.

We report herein our preliminary results on the syntheses and thermal isomerizations of 2-2-{[2-(*sec*-amino)benzyl](methyl) amino}- and {2-[2-(*sec*-amino)phenoxy]benzylidene}malononitriles, bridged with a methylamino-*N*-methyl group or an oxygen between the phenyl rings bearing an amino and vinyl moiety in *ortho*- and *ortho*′-positions.

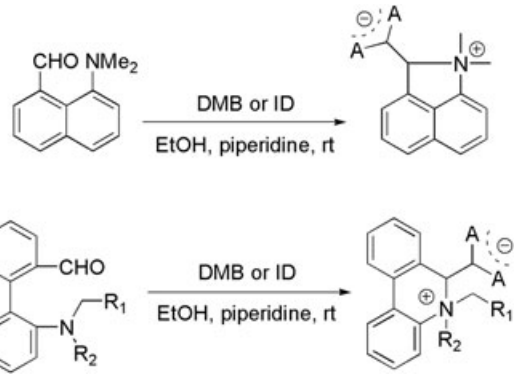


Figure 3. Formation of zwitterionic phenantridium and benzo[*d*,*e*] quinolinium derivatives. [DMB: 1,3-dimethylbarbituric acid, ID: 1*H*-indene-1,3(2*H*)-dione]

EXPERIMENTAL

General

All reagents and solvents were purchased from commercial sources and were utilized without further purification. Melting points were determined on a Büchi-540 (Büchi Labortechnik AG, Flawil, Switzerland) capillary melting point apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded at ambient temperature, in the solvent indicated, with a Varian Mercury Plus spectrometer (Agilent Technologies, Santa Clara, CA, USA) at a frequency of 400 or 100 MHz or with a Bruker 500 MHz (Bruker Biospin,

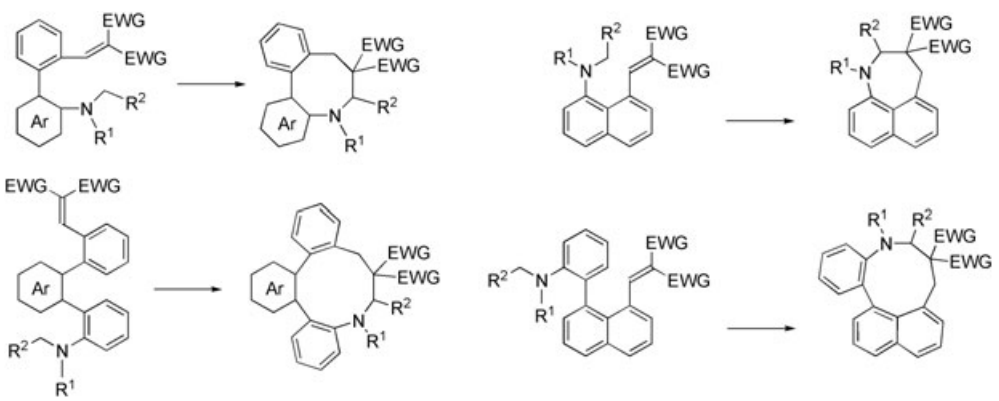


Figure 2. Synthesis of medium and macrocyclic ring systems by *tert*-amino effect

Rheinstetten, Germany) spectrometer, at a frequency of 500 or 125 MHz, and are reported in parts per million (ppm). Spectra were recorded at 500 MHz (^{1}H) or 125 MHz (^{13}C), if not indicated otherwise. Chemical shifts are given on the δ-scale relative to tetramethylsilane or the residual solvent signal as an internal reference. In reporting spectral data, the following abbreviations were used: s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet doublet, dm = doublet multiplet, tm = triplet multiplet, and br = broad. For structure elucidation, one-dimensional ^{1}H, ^{13}C, DEPT, two-dimensional ^{1}H, ^{1}H-COSY, ^{1}H, ^{13}C-HSQC, ^{1}H, ^{13}C-HMBC measurements were run. Elemental analyses were performed on a Carlo Erba 1012 apparatus (Thermo Fisher Scientific, Milan, Italy), analyses indicated by the symbols of the elements affording satisfactory results. Microwave (MW) irradiation experiments were carried out in a monomode CEM-Discover MW reactor (CEM Corporation, Matthews, NC, USA) by using the standard configuration as delivered, including proprietary software. The experiments were executed in 10 mL MW process vials with control of the temperature by infrared detection. After completion of the reaction, the vial was cooled to 50 °C by air jet cooling. For flash column chromatography purification, Kieselgel 60 (Merck 0.040–0.063 mm) (Merck KGaA, Darmstadt, Germany) was used; for thin layer chromatography (TLC) analysis, silica gel 60F_{254} (Merck) plates were applied. Solvent mixtures used for chromatography are always given in a v/v ratio. The structures of all compounds were consistent with their analytical and spectroscopic data. Compounds **2a**, **2b**, **3a**, **3b**, **4a**, **4b**, and **9** were prepared according to the literature procedures cited[25,26] and had melting points and/or spectral data identical with the published values.

X-ray diffraction studies

A good-looking single crystal of the compound was fixed on the top of a glass fiber using epoxy glue. Data were collected at 293(1) K, Enraf Nonius MACH3 diffractometer (Bruker Nonius, Delft, Netherlands), Mo Kα radiation $\lambda = 0.71073$ nm, ω motion. Raw data were evaluated using the XCAD4 software;[27] the structure was solved using direct methods by the SIR-92 software[28] and refined on F^2 using SHELX-97[29] program. Refinement was performed anisotropically for nonhydrogen atoms. Hydrogen atoms were placed into geometric position. The structure also contained a disordered hexane molecule. Figures were prepared with the WINGX-97 suite.[30] The PLATON program[31,32] was used for crystallographic calculations.

Differential scanning calorimetry measurements

The thermoanalytical examinations of the materials were carried out with a Mettler-Toledo TG/DSC1 instrument (Mettler Toledo AG, Greifensee, Switzerland). During the measurements, the start temperature was 25 °C, the end temperature was 500 °C, and the applied heating rate was 10 °C/min. Nitrogen atmosphere was used. A 2–10 mg sample was measured into aluminum pans (100 μL). The curves were evaluated with STARe software (Mettler Toledo AG, Greifensee, Switzerland).

Computational chemistry

Semiempirical PM3 and density functional theory (DFT) calculations were carried out by using Schrödinger's Jaguar program package (Jaguar, version 7.8, Schrödinger, LLC, New York, NY, USA, 2011) on HP (Z800) workstation. Starting geometries were obtained with ConfGen Advanced module (with standard settings), followed by PM3 level optimization. For DFT, gradient-corrected functional BP86 model and hybrid functional B3P86 model[33–38] with a 6-31G** basis set in vacuum were used.

Synthesis

Synthesis of N,N-dialkyl-2-[(methylamino)methyl]anilines

To 40 wt% aq. methylamine (67 mL, 776.00 mmol) at −10 °C, a solution of the 2-(chloromethyl)-*N*,*N*-dialkylanilines (19.42 mmol, for **5a**: 2-(chloromethyl)-*N*,*N*-dimethylaniline hydrochloride – 4.00 g, for **5b**: 1-[2-(chloromethyl)phenyl] piperidine hydrochloride – 4.78 g) in EtOH (70 mL) was added dropwise. The mixture was stirred at −10 °C for 2 h (monitored by TLC). The solvent was removed *in vacuo*, 30 mL H_2O was added, and the mixture was extracted with EtOAc (3 × 30 mL). The organic layer was discarded, and the pH of the aqueous phase was adjusted to 13 with 2 M NaOH. The aqueous phase was extracted with EtOAc (5 × 30 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and evaporated to dryness.

*N,N-Dimethyl-2[(methylamino)methyl]aniline (**5a**)*

The crude product was purified by fractionary distillation under reduced pressure (102 °C, 5 mmHg). Colorless oil (1.28 g, 40%). ^{1}H NMR ($CDCl_3$) δ (ppm): 2.44 (s, 3H, CH_3), 2.70 (s, 6H, $N(CH_3)_2$), 3.83 (s, 2H, CH_2), 7.02–7.06 (m, 1H, Ar–H), 7.11 (dd, 1H, J = 1.0, 8.0 Hz, Ar–H), 7.20–7.25 (m, 1H, Ar–H), 7.31 (dd, 1H, J = 1.5, 7.5 Hz, Ar–H). ^{13}C NMR ($CDCl_3$) δ (ppm): 36.8, 45.7, 52.9, 119.9, 124.0, 128.3, 130.3, 134.9, 153.3. For elemental analysis, HCl salt of the product was formed. Anal. ($C_{10}H_{16}N_2 \times 2.5$ HCl) C, H, N.

*N-Methyl-1-(2-piperidin-1-ylphenyl)methanamine (**5b**)*

Colorless oil (2.42 g, 61%). ^{1}H NMR (DMSO-d_6) δ (ppm): 1.45–1.55 (m, 2H, CH_2), 1.60–1.68 (m, 4H, CH_2), 2.30 (s, 3H, CH_3), 2.75–2.85 (m, 4H, CH_2), 3.66 (s, 2H, CH_2), 6.97–7.10 (m, 1H, Ar–H), 7.04 (dm, 1H, J = 1.0, 7.0 Hz, Ar–H), 7.15–7.19 (m, 1H, Ar–H), 7.36 (dm, 1H, J = 7.0 Hz, Ar–H). ^{13}C NMR (DMSO-d_6) δ (ppm): 23.9, 26.2, 36.1, 50.6, 53.5, 119.2, 122.8, 127.2, 129.1, 134.5, 152.3. For elemental analysis, HCl salt of the product was formed. Anal. ($C_{13}H_{20}N_2 \times 2$ HCl) C, H, N.

Synthesis of 2-{[2-(sec-amino)benzyl](methyl)amino}benzaldehydes

A suspension of the amine compound (4.29 mmol, for **6a**: **5a** – 705 mg, for **6b**: **5b** – 876 mg), 2-fluorobenzaldehyde (4.29 mmol, 0.45 mL), and K_2CO_3 (6.54 mmol, 904 mg) in 12 mL dimethylformamide was heated at 110 °C for 7 h (monitored by TLC). The mixture was then cooled down to room temperature and filtered. The solvent was removed *in vacuo*, and the crude product obtained was purified by flash column chromatography on silica gel.

*2-{[2-(Dimethylamino)benzyl](methyl)amino}benzaldehyde (**6a**)*

Column chromatography: *n*-hexane/EtOAc 9:1, R_f = 0.16. Yellow oil (1.07 g, 93%). ^{1}H NMR ($CDCl_3$) δ (ppm): 2.63 (s, 6H, $N(CH_3)_2$), 2.86 (s, 3H, CH_3), 4.46 (s, 2H, CH_2), 6.98–7.02 (m, 1H, Ar–H), 7.02–7.06 (m, 1H, Ar–H), 7.11 (dm, 1H, J = 8.0 Hz, Ar–H), 7.12 (dm, 1H, J = 8.0 Hz, Ar–H), 7.21–7.26 (m, 1H, Ar–H), 7.41–7.46 (m, 2H, Ar–H), 7.80 (dm, 1H, J = 7.5 Hz, Ar–H), 10.33 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$) δ (ppm): 43.4, 45.6, 58.1, 119.6, 120.0, 121.5, 124.0, 128.1, 128.5, 129.2, 130.7, 132.4, 135.2, 153.5, 156.6, 192.0. For elemental analysis, HCl salt of the product was formed. Anal. ($C_{17}H_{20}N_2O \times 2.5$ HCl) C, H, N.

*2-[(2-Piperidin-1-ylbenzyl)(methyl)amino]benzaldehyde (**6b**)*

Column chromatography: *n*-hexane/EtOAc 4:1, R_f = 0.65. Yellow oil (1.26 g, 95%). ^{1}H NMR ($CDCl_3$) δ (ppm): 1.50–1.60 (m, 2H, CH_2), 1.60–1.70 (m, 4H, CH_2), 2.75–2.85 (m, 4H, CH_2), 2.88 (s, 3H, CH_3), 4.44 (s, 2H, CH_2), 6.97–7.02 (m, 1H, Ar–H), 7.01–7.06 (m, 1H, Ar–H), 7.10 (dm, 1H, J = 8.0 Hz, Ar–H), 7.11 (dm, 1H, Ar–H), 7.20–7.25 (m, 1H, Ar–H), 7.39 (dm, 1H, J = 7.5 Hz, Ar–H), 7.40–7.45 (m, 1H, Ar–H), 7.79 (dm, 1H, Ar–H), 10.30 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$) δ (ppm): 24.9, 27.2, 43.7, 55.0, 57.4, 119.6, 120.7, 121.2, 124.1, 128.0, 128.6, 129.2, 130.8, 132.9, 135.2, 153.7, 156.5, 192.0. Anal. ($C_{20}H_{24}N_2O$) C, H, N.

Synthesis of 2-(2-{[2-(sec-amino)benzyl](methyl)amino}benzylidene) malononitriles

A mixture of the benzaldehyde compound (4.86 mmol, for **7a**: **6a** – 1.30 g, for **7b**: **6b** – 1.50 g) and malononitrile (4.86 mmol, 321 mg) in 24 mL EtOH was stirred for 3 h at room temperature.

*2-(2-{[2-(Dimethylamino)benzyl](methyl)amino} benzylidene) malononitrile (**7a**)*

Work-up: the solvent was removed *in vacuo*, and the crude product obtained was purified by flash column chromatography on silica gel (eluent: *n*-hexane/EtOAc 4:1, $R_f = 0.36$). Orange oil (1.32 g, 86%). ^{1}H NMR ($CDCl_3$) δ (ppm): 2.61 (s, 6H, CH_3), 2.82 (s, 3H, CH_3), 4.29 (s, 2H, CH_2), 7.03–7.11 (m, 2H, Ar–H), 7.14 (dm, 2H, $J = 8.5$ Hz, Ar–H), 7.24–7.29 (m, 2H, Ar–H), 7.45–7.49 (m, 1H, Ar–H), 8.01 (dm, 1H, $J = 8.0$ Hz, Ar–H), 8.12 (s, 1H, CH). ^{13}C NMR ($CDCl_3$) δ (ppm): 43.5, 45.7, 58.4, 80.7, 113.7, 115.0, 120.6, 120.6, 122.9, 124.2, 125.0, 129.1, 129.6, 129.9, 132.0, 135.3, 153.5, 155.8, 159.0. For elemental analysis, HCl salt of the product was formed. Anal. ($C_{20}H_{20}N_4 \times 2.5$ HCl) C, H, N.

*2-(2-{[2-(Piperidin-1-yl)benzyl](methyl)amino}benzylidene)malononitrile (**7b**)*

Work-up: the precipitated crystals were filtered off and washed with EtOH. Orange crystals (1.56 g, 90%), melting point (mp) 95–96 °C. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.50–1.60 (m, 2H, CH_2), 1.65–1.70 (m, 4H, CH_2), 2.65–2.75 (m, 4H, CH_2), 2.85 (s, 3H, CH_3), 4.26 (s, 2H, CH_2), 7.03–7.14 (m, 3H, Ar–H), 7.19 (dm, 1H, $J = 8.5$ Hz, Ar–H), 7.22–7.28 (m, 2H, Ar–H), 7.45–7.50 (m, 1H, Ar–H), 8.00 (dm, 1H, $J = 8.0$ Hz, Ar–H), 8.03 (s, 1H, CH). ^{13}C NMR ($CDCl_3$) δ: 24.8, 27.3, 44.2, 55.0, 57.5, 80.6, 113.7, 115.0, 120.7, 121.0, 122.9, 123.0, 124.4, 125.0, 129.1, 129.4, 129.9, 132.6, 135.3, 153.6, 155.7, 158.9. Anal. ($C_{23}H_{24}N_4$) C, H, N.

Cyclization of 2-(2-{[2-(sec-amino)benzyl](methyl)amino}benzylidene) malononitriles

The vinyl precursors (0.84 mmol, for **8a**: **7a** – 266 mg, for **8b**: **7b** – 299 mg) in a 10 mL MW process vial were irradiated at the temperature and for the reaction time indicated (at 250 W maximum power level). The vial was subsequently cooled to ambient temperature, and 15 mL CH_2Cl_2 was added. The mixture was washed with H_2O (3 × 15 mL), and the organic layer was dried ($MgSO_4$), filtered, and evaporated to dryness to afford the pure products.

*2-(2-(Dimethylamino)phenyl)-1-methyl-1,2-dihydroquinoline-3,3 (4H)-dicarbonitrile (**8a**)*

Heating: 135 °C, 10 min. White crystals (266 mg, 100%), mp 170–172 °C. ^{1}H NMR ($CDCl_3$) δ (ppm): 2.74 (s, 6H, CH_3), 2.97 (s, 3H, CH_3), 3.35 (d, 1H, $J = 16.0$ Hz, CH_2), 3.42 (d, 1H, $J = 16.0$ Hz, CH_2), 5.74 (s, 1H, CH), 6.78 (dm, 1H, $J = 8.0$ Hz, Ar–H), 6.79–6.82 (m, 1H, Ar–H), 7.04–7.09 (m, 3H, Ar–H), 7.25–7.30 (m, 1H, Ar–H), 7.33–7.39 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$) δ: 34.8, 35.5, 38.8, 46.7, 61.1, 112.1, 114.5, 115.5, 116.2, 118.3, 122.7, 126.0, 127.9, 129.8, 130.2, 131.3, 132.5, 144.6, 154.8. Anal. ($C_{20}H_{20}N_4$) C, H, N.

*1-Methyl-2-(2-(piperidin-1-yl)phenyl)-1,2-dihydroquinoline-3,3(4H)-dicarbonitrile (**8b**)*

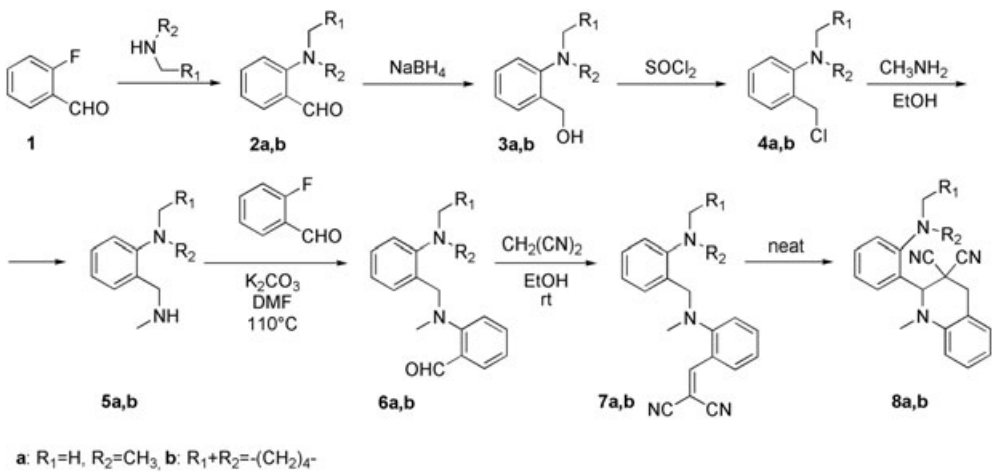
Heating: 130 °C, 10 min. White crystals (299 mg, 100%), mp 167–169 °C. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.50–1.80 (m, 6H, CH_2), 2.70–3.00 (m, 4H, CH_2), 2.95 (s, 3H, CH_3), 3.32 (d, 1H, $J = 16.0$ Hz, CH_2), 3.40 (d, 1H, $J = 16.0$ Hz, CH_2), 5.63 (s, 1H, CH), 6.78 (dm, 1H, $J = 7.5$ Hz, Ar–H), 6.78–6.82 (m, 1H, Ar–H), 7.01–7.08 (m, 3H, Ar–H), 7.25–7.30 (m, 2H, Ar–H), 7.33–7.37 (m, 1H, Ar–H). ^{13}C NMR ($CDCl_3$) δ: 24.8, 27.3, 34.8, 35.5, 38.8, 55.0, 61.3, 112.1, 114.6, 115.2, 116.2, 118.3, 123.0, 125.8, 127.8, 129.8, 130.2, 131.2, 132.5, 144.6, 154.6. Anal. ($C_{23}H_{24}N_4$) C, H, N.

*2-[2-(Pyrrolidin-1-yl)phenoxy]benzaldehyde (**10**)*

To a solution of 2-(pyrrolidin-1-yl)phenol[12] (15.00 mmol, 2.45 g) in *N,N*-dimethylacetamide (15 mL), 2-fluorobenzaldehyde (15.00 mmol, 1.58 mL) and K_2CO_3 (30.00 mmol, 4.15 g) were added. The mixture was heated at 160 °C (oil temperature) under argon atmosphere for 1.5 h. To the cooled reaction mixture, EtOAc (20 mL) was added. The organic phase was washed with H_2O (1 × 20 mL) and aq. saturated Na_2CO_3 solution (1 × 20 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated to dryness. The crude product obtained was purified by flash column chromatography on silica gel (toluene). Yellow crystals (1.98 g, 51%), mp 82–83 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.82–1.86 (m, 4H, CH_2), 3.31–3.36 (m, 4H, CH_2), 6.69 (dm, 1H, $J = 8.0$ Hz, Ar–H), 6.74 (tm, 1H, $J = 7.6$ Hz, 1H, Ar–H), 6.82 (dm, 1H, $J = 8.0$ Hz, Ar–H), 6.94 (dm, 1H, $J = 8.0$ Hz, Ar–H), 7.04–7.15 (m, 2H, Ar–H), 7.40–7.45 (m, 1H, Ar–H), 7.90 (dm, 1H, $J = 8.0$ Hz, Ar–H), 10.64 (d, 1H, $J = 0.7$, CHO). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 26.0, 50.7, 116.3, 116.7, 118.5, 122.4, 123.5, 126.0, 126.8, 128.9, 136.5, 142.7, 142.9, 162.0, 190.3. Anal. ($C_{17}H_{17}NO_2$) C, H, N.

*{2-[2-(Pyrrolidin-1-yl)phenoxy]benzylidene}propanedinitrile (**11**)*

To a solution of the aldehyde (**10**) (2.00 mmol, 535 mg) in EtOH (2.50 mL), malononitrile (2.00 mmol, 132 mg,) and a few drops of piperidine were added. The mixture was stirred at room temperature until the starting material had been consumed (monitored by TLC, 2 h). The precipitated crystals were filtered off and washed with 5 × 1 mL EtOH to afford the analytically pure product. Orange crystals (410 mg, 65%), mp 92–93 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.83–1.92 (m, 4H, CH_2), 3.23–3.32 (m, 4H, CH_2), 6.70 (dm, 1H, $J = 8.0$ Hz, Ar–H), 6.71–6.78 (m, 1H, Ar–H), 6.83 (dm, 1H, $J = 8.0$ Hz, Ar–H), 6.86 (dm, 1H, $J = 8.0$ Hz, Ar–H), 7.09–7.18 (m, 2H, Ar–H), 7.41–7.48 (m, 1H, Ar–H), 8.29 (dm, 1H, $J = 8.0$ Hz, Ar–H), 8.46 (s, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 26.0, 50.7, 82.7, 113.6, 114.9, 116.6, 116.6, 118.8, 121.2, 123.0, 123.4, 127.3, 129.2, 137.0, 142.3, 142.8, 154.8, 159.2. Anal. ($C_{20}H_{17}N_3O$) C, H, N.



Scheme 1. Synthesis and cyclization of 2-(2-{[2-(*sec*-amino)benzyl](methyl)amino}benzylidene)malononitriles

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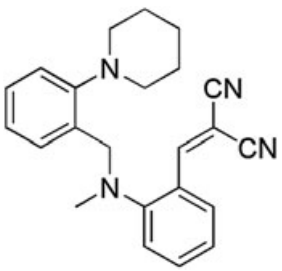
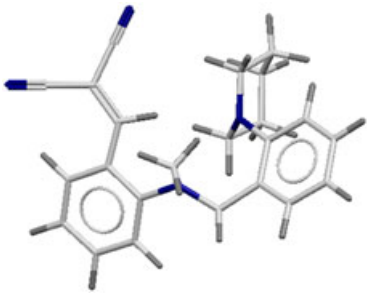
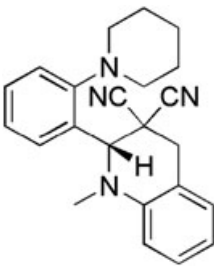
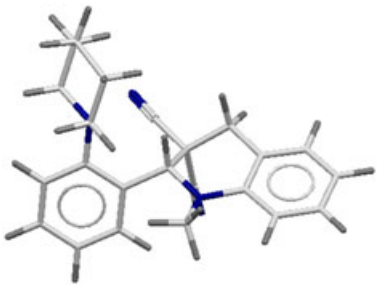
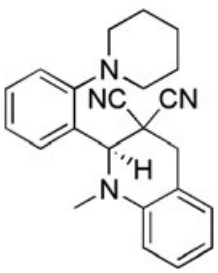
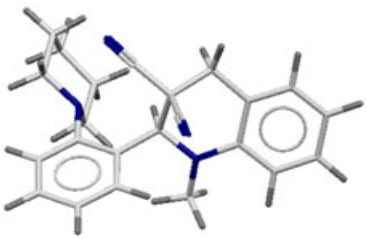
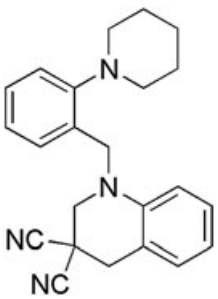
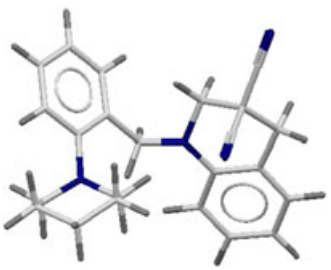
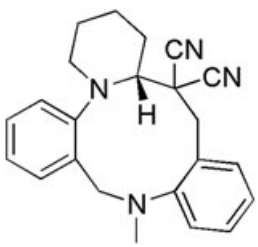
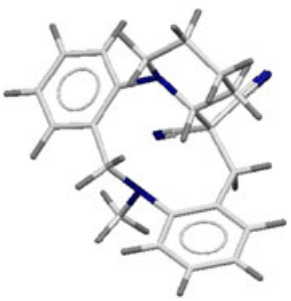
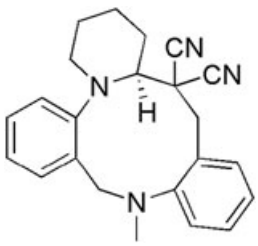
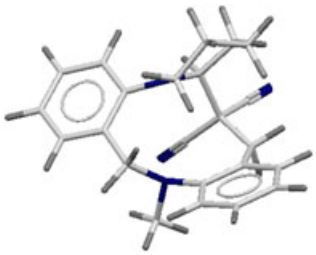
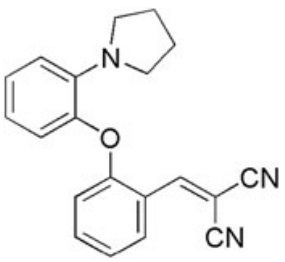
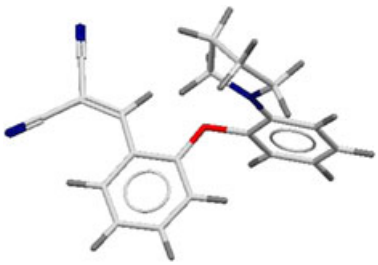
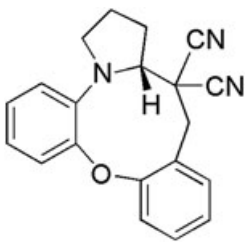
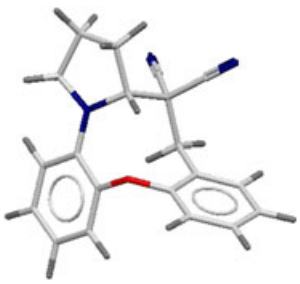
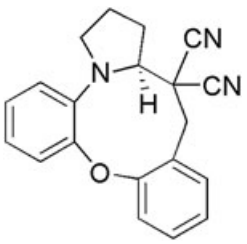
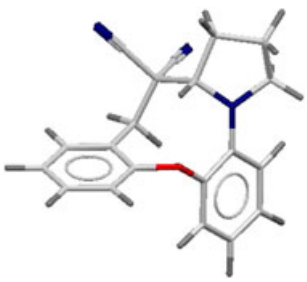
Table 1. Enthalpies of reaction determined by differential scanning calorimetry (DSC) (ΔH_r) and by calculation ($\Delta\Delta H_f = \Delta H_{f\,pr} - \Delta H_{f\,st}$)

Compound	Structure	Optimized structure	T_m (°C)[a]	T_r (°C)[b]	ΔH_r (kcal/mol)[c]	$\Delta\Delta H_f$ (kcal/mol)[d]
7b			96.3	NA	NA	NA
8b-*R*			169.7	161.4	−11.26	−15.15
8b-*S*			169.7	161.4	−11.26	−15.13
13			NA	NA	NA	−14.76
14-*R*			NA	NA	NA	4.98

(*Continues*)

Table 1. *(Continued)*

Compound	Structure	Optimized structure	T_m (°C)[a]	T_r (°C)[b]	ΔH_r (kcal/mol)[c]	$\Delta\Delta H_f$ (kcal/mol)[d]
14-*S*			NA	NA	NA	6.74
11			93.9	NA	NA	NA
12-*R*			171.99	169.9	−8.58	−6.04
12-*S*			171.99	169.9	−8.58	−6.25

[a] T_m corresponds to the melting temperature (DSC endothermic peak).
[b] T_r corresponds to the temperature of cyclization (DSC exothermic peak).
[c] ΔH_r is the enthalpy of reaction.
[d] $\Delta\Delta H_f$ corresponds to the difference of calculated heats of formation as obtained by DFT method (B3P86).

5,6,7,7a-Tetrahydrodibenzo[e,h]pyrrolo[1,2-a]oxazonine-8,8(9 H)-dicarbonitrile (**12**)

A solution of the vinyl precursor (**11**, 2.00 mmol, 631 mg) in 1 mL dry DMSO was heated at 100 °C for 15 min. The reaction mixture was subsequently cooled to ambient temperature and poured into CH_2Cl_2 (15 mL). The organic layer was washed with H_2O (3 × 15 mL), dried ($MgSO_4$), filtered, and evaporated to dryness. The residue obtained was purified by flash column chromatography on silica gel with *n*-hexane:EtOAc 4:1 eluent. White crystals (133 mg, 21%), mp 172–174 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.97–2.09 (m, 1H, CH_2), 2.24–2.36 (m, 2H, CH_2), 2.56–2.65 (m, 1H, CH_2), 3.03 (d, 1H, J = 14.8 Hz, CH_2), 3.41–3.48 (m, 1H, CH_2), 3.74 (d, 1H, J = 14.8 Hz, CH_2), 3.87–3.95 (m, 1H, CH_2), 5.35 (br s, 1H, CH), 6.78–6.83 (m, 1H, Ar–H), 6.89 (dm, 1H, J = 8.0 Hz, Ar–H), 6.92 (dm, 1H, J = 8.0 Hz, Ar–H), 7.06–7.11 (m, 1H, Ar–H), 7.14–7.18 (m, 2H, Ar–H), 7.29 (dm, 1H, J = 8.0 Hz, Ar–H), 7.37–7.43 (m, 1H, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 23.2, 32.7, 38.5, 45.6, 51.9, 62.9, 114.6, 116.3, 118.8, 121.3, 122.9, 122.9, 124.1, 125.5, 126.6, 131.4, 135.0, 140.4, 146.1, 156.3. Anal. ($C_{18}H_{15}N_3O$) C, H, N.

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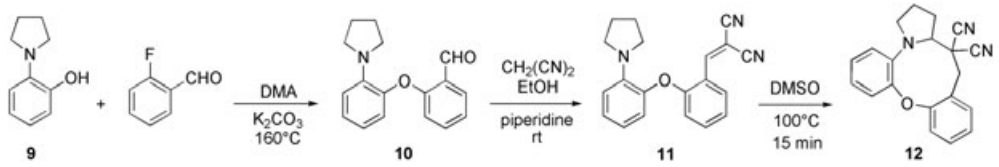

Scheme 2. Synthesis and cyclization of {2-[2-(*sec*-amino)phenoxy]benzylidene}malononitriles

RESULTS AND DISCUSSION

Synthesis and isomerization of 2-(2-{[2-(*sec*-amino)benzyl](methyl)amino}benzylidene)malononitriles

2-(2-{[2-(*sec*-Amino)benzyl](methyl)amino}benzylidene)malononitriles were prepared in several steps.[25] Thus, 2-(chloromethyl)-*N*,*N*-dialkylanilines (**4a**,**b**) obtained via a known procedure from 2-fluorobenzaldehyde were reacted with methylamine to give the corresponding *N*,*N*-dialkyl-2-[(methylamino)methyl]anilines (**5a**,**b**). Arylation with 2-fluorobenzaldehyde afforded (2-*sec*-amino)benzylamines **6a**,**b**, which upon reacting with malononitrile under mild conditions led to vinyl derivatives **7a**,**b** (Scheme 1).

Compounds **7a**,**b**, may *a priori* cyclize in three pathways, either with involvement of methylene-carbon, *N*-methyl-carbon, or the α-carbon of the *sec*-amino group attached to the other phenyl ring (leading to compounds **8**, **13**, or **14**, respectively, as listed in Table 1). Not fully unexpectedly, cyclization, following our solvent-free protocol, exclusively took place via the first route, affording the product with six-membered ring in excellent yield.

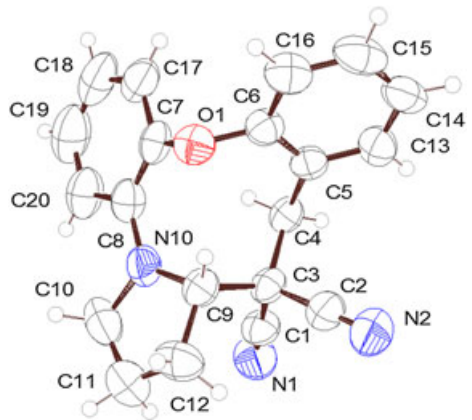

Figure 4. ORTEP view and numbering scheme of **12**; only one molecule from the asymmetric unit is shown. The other enantiomer from the asymmetric unit was omitted because of clarity. Moreover, as the space group is centric, the unit cell contains the exact mirror images of both enantiomers

Synthesis and cyclization of (2-[2-(*sec*-amino)phenoxy]benzylidene)malononitriles

2-Pyrrolidinophenoxybenzaldehyde (**10**) was prepared from 2-fluorobenzaldehyde with 2-pyrrolidinophenol (**9**)[26] (Scheme 2). Its subsequent Knoevenagel condensation with malononitrile afforded **11**. In DMSO solution at 100 °C, the expected oxazonine **12**, representing a novel ring system, could be isolated, albeit only in modest yield, presumably because of decomposition.

Structure of **12** was unambiguously confirmed by X-ray crystallography. Upon cyclization – also for compounds **8a**,**b** – formation of racemic mixtures may be expected. Indeed, for compound **12**, two molecules were observed in the asymmetric unit, with R or S configuration at the stereogenic carbon, respectively. Although the inversion of the pyrrolidino nitrogen might result in detectable isomers, interestingly, it was found to be planar, with location in plane of the aromatic ring (Fig. 4). The angle of planes of two aromatic rings is around 74° and 69° for the two molecules present in the asymmetric unit, respectively. Nine-membered heterocycles are hardly represented in the Cambridge Structural Database[39] (moreover, a direct structural comparison is difficult, because of high fluxionality of such systems).

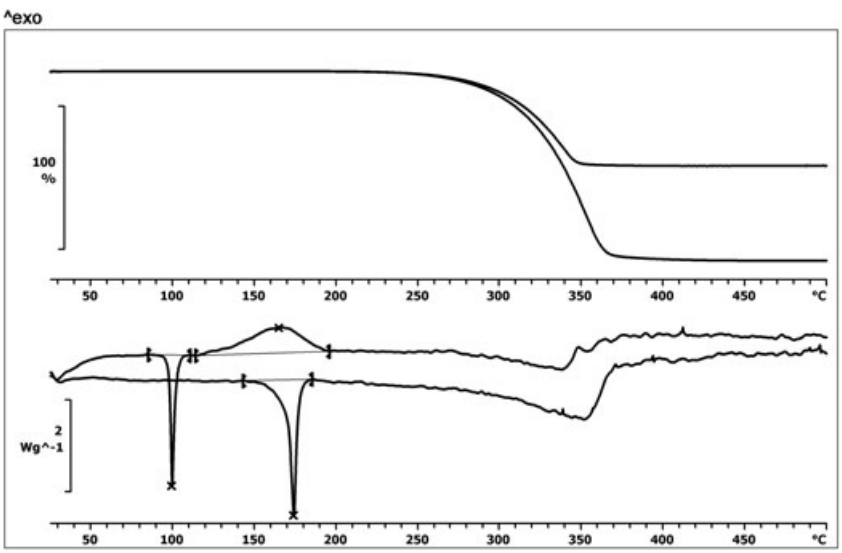

Figure 5. The thermogravimetry (upper) and differential scanning calorimetry (lower) curves of compounds **7b** and **8b**

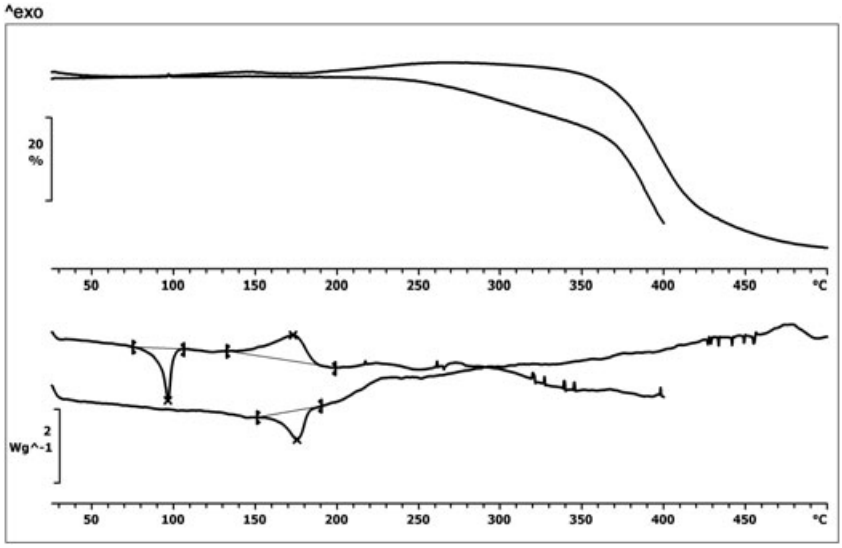

Figure 6. The thermogravimetry (upper) and differential scanning calorimetry (lower) curves of compounds **11** and **12**

Thermochemical studies

Our previous differential scanning calorimetry (DSC) study of *tert*-amino effect[40] showed the applicability of this method for detection of the ring closure. Calculations (PM3, DFT) and experimental data (DSC) suggested that the cyclization is an exothermic process that could also be well detected on the DSC curves.

Differential scanning calorimetry measurements complemented by parallel thermal gravimetry (between room temperature and 500 °C) were run for **7b–8b** and **11–12** (Figs 5 and 6) to assess whether cyclization could be monitored with this method for novel scaffolds. In the temperature range of the endothermic and exothermic peaks, no significant weight loss – that is, decomposition – was observed. The peaks corresponding to the melting points could be identified as endothermic peaks at 96.3 and 93.9 °C, respectively. The second exothermic peaks observed might indicate that cyclization did take place upon heating; that is, it corresponds to the temperature of ring closure. TLC monitoring and ^{1}H NMR spectra recorded from the samples following the DSC experiment confirmed that only thermal ring closure occurred in the case of **7b**, whereas in the case of **11**, considerable decomposition could be detected. Integrals of the areas under the exothermic peaks (related to cyclization) provide the enthalpy changes of the reactions. These experimental enthalpy changes together with the calculated ones are listed in Table 1. The calculated heat of reaction values were determined as the differences of heat of formation of fused products and that of the starting vinyl compounds (full geometrical optimization was carried out for all compounds). In the case of **7b**, the two potential alternative products (with *N*-methyl: **13**, and with *ortho*′ *tert*-amino moiety: **14**) were included as well.

CONCLUSION

In conclusion, two novel types of *tert*-amino effect related reactions have been investigated. The aminomethyl- or oxygen-bridged biphenyls possessing vinyl and amino group in *ortho*- and *ortho*′-positions undergo cyclization with C–C bond formation in two different pathways. The aminomethyl-bridged compounds **7a**,**b**, possessing more than one hydrogen possibly involved in isomerization, led to tetrahydroquinolines **8a**,**b** with the involvement of benzylic hydrogen. In the case of the oxygen-bridged vinyl compound **11**, the expected novel dibenzoxazonine ring system **12** was obtained. These finding may indicate on the one hand an inherent migratory aptitude of hydrogen and a wider scope of ring closure reactions via *tert*-amino effect.

We also found that DSC may be a suitable method for identification and characterization of thermal isomerization reactions.

Acknowledgements

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