tert-Amino Effect in *peri*-Substituted Naphthalenes: Syntheses of Naphthazepine and Naphthazonine Ring Systems

Ágota Anna Földi,[a] Krisztina Ludányi,[b] Attila Csaba Bényei,[c] Péter Mátyus*[a]

[a] Department of Organic Chemistry, Semmelweis University, Hőgyes Endre utca 7., 1092 Budapest, Hungary
Fax +36(1)2170851; E-mail: peter.matyus@szerves.sote.hu

[b] Department of Pharmacy, Semmelweis University, Hőgyes Endre utca 7., 1092 Budapest, Hungary

[c] Department of Chemistry, Laboratory for X-ray Diffraction, University of Debrecen, Egyetem tér 1., 4010 Debrecen, Hungary

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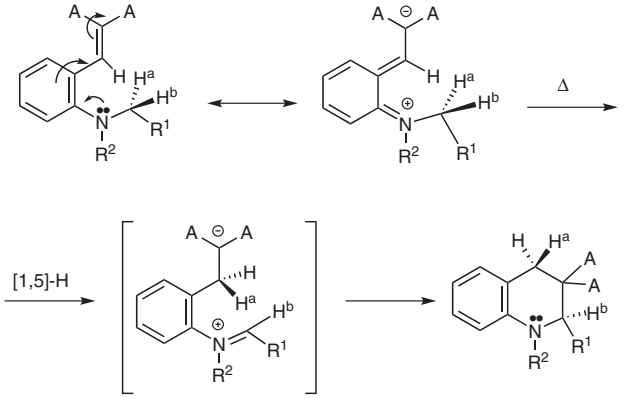
Dedicated to Professor Tamás Roska on the occasion of his 70th birthday

Abstract: Novel straightforward syntheses of naphtho-fused azepines and benzazonine via *tert*-amino effect are described. Starting from 1-naphthylamine, 8-*N*,*N*-dialkylaminonaphthalene-1-carbaldehydes could be obtained in two steps. The aldehyde was prepared by a Suzuki reaction of 8-bromonaphthalene-1-carbaldehyde with *ortho*-pyrrolidinophenylboronic acid. Treatment of aldehydes with active methylene compounds afforded naphthazepines and novel benzazonine ring system, respectively, through rearrangement of isolable vinyl intermediates or benzo[*de*]quinolinium derivatives or without isolation of any intermediates. A mechanistic investigation supports an intramolecular hydride transfer for the ring closure to azepine or azonine. Our results indicate that the *tert*-amino effect may provide a valuable approach to the synthesis of *ortho*- and *peri*-fused aza-ring systems.

Key words: *tert*-amino effect, naphthazepine, naphthazonine, benzo[*d*,*e*]quinolinium, *peri*-interaction

The term '*tert*-amino effect' was introduced by Meth-Cohn and Suschitzky nearly forty years ago, to describe thermal rearrangement reactions of *ortho*-substituted *tert*-anilines via cyclization to benzofused aza-ring systems.[1] Seven types of the *tert*-amino effect have been distinguished so far, according to the size of the ring formed and its mode of formation.[2] One version of type 2 reactions, the isomerization reaction of *tert*-anilines with an *ortho*-vinyl group and their heterocyclic analogues has received much attention, due to its high synthetic value to obtain biologically useful tetrahydroquinolines and related fused ring systems with predictable regio- and stereochemistry.[3a–3f] This type of *tert*-amino effect can occur in two steps: the rate-limiting first step involves a hydrogen migration from the *N*-methylene carbon to the α-vinyl carbon affording a 1,5-dipolar intermediate that cyclizes in the second step to a tetrahydropyrido-fused system with the formation of a new carbon–carbon σ-bond (Figure 1). An additional feature of such reactions is the requirement of strongly electron-withdrawing substituents in the vinyl group to stabilize the negative end of the dipolar intermediate. In context of the hydrogen migration, a sigmatropic [1,5]-hydrogen shift and an ionic mechanism with hydride transfer have been proposed.



A: electron-withdrawing group

Figure 1 Isomerization via type 2 *tert*-amino effect

In our studies, kinetics, thermodynamics, steric features, the synthetic scope, and methodological limitations of this type of *tert*-amino effect have been investigated and various types of pyrido-fused diazines have been prepared.[4a–f] An impressive number and diversity of very recent examples,[5a–e] illustrate further the synthetic potential of type 2 *tert*-amino effect.

Interestingly, only very few isomerization reactions have been reported, which led to the formation of a seven-membered or larger ring.[6] In our approaches, vinyl-substituted bi- or triaryl-*tert*-amines **A** and **B** could be cyclized to diarene-fused azocines[7a] and triarene-fused azecines,[7b] respectively, via type 2 *tert*-amino effect (Figure 2). Following this line, we also decided to study *ortho*-fused aromatic ring systems, the prototype of which is naphthalene, possessing key functionalities in *peri*-positions.

Herein we report on novel extensions of the *tert*-amino effect to 1-dialkylamino- and 1-(2-dialkylaminophenyl)-8-vinylnaphthalenes, **C** and **D**, respectively, to open new routes to *ortho*- and *peri*-fused naphthazepine and naphthazonine ring systems (Figure 2); these compounds show, in turn, some structural resemblances to naphthalenes **I** and **II** (Figure 3) and related compounds exhibiting anti-HIV activity.[8]

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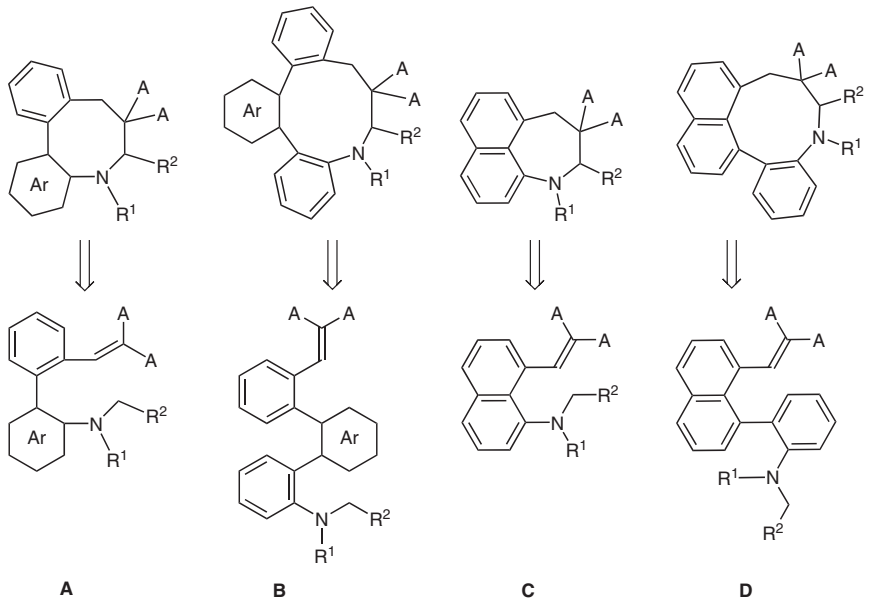


Figure 2 Some recent and new extensions of type 2 *tert*-amino effect: syntheses of diarene-fused azocines, triarene-fused azecines, and naphthalene-fused azepine or azonine ring systems

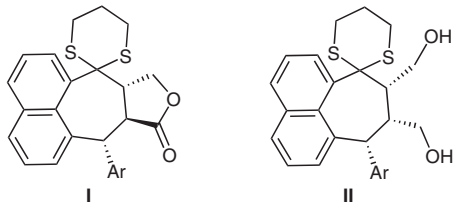
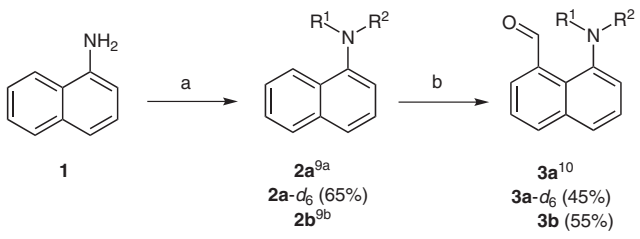


Figure 3 Synthetic lignan analogues **I** and **II** evaluated as anti-HIV agents

In our study, acyclic and cyclic amino and vinyl substitutents were employed. Synthesis of vinyl derivatives was accomplished in three steps, starting from commercially available 1-naphthylamine (**1**). Its dimethylation according to the published protocol led to dimethylaminonaphthalene (**2a**).[9a] Pyrrolidino derivative **2b**[9b] was obtained by alkylation with 1,4-dibromobutane. The *peri*-selective formylation afforded aldehydes **3a**[10] and **3b** (Scheme 1).



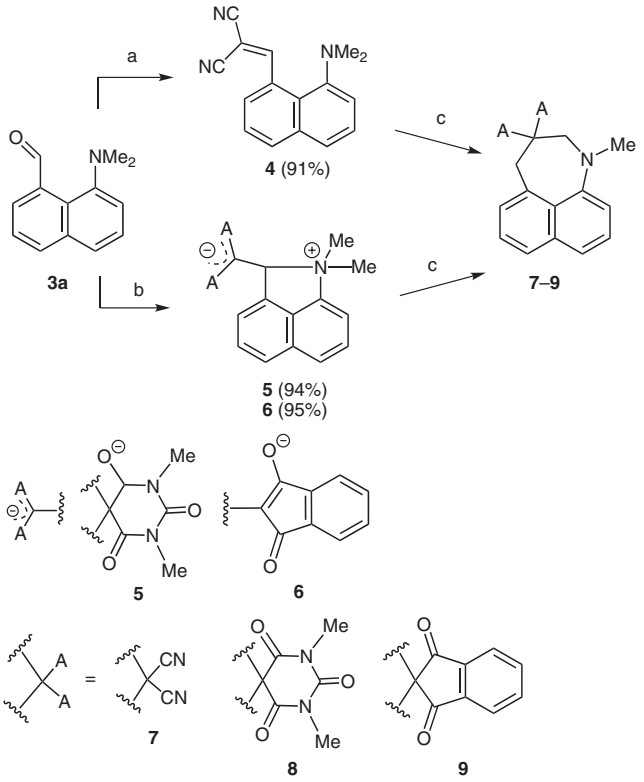
2a, **3a** R^1, R^2 = Me
2a-d_6, **3a**-d_6 R^1, R^2 = CD_3
2b, **3b** $R^1 + R^2 = (CH_2)_4$

Scheme 1 *Reagents and conditions*: for **2a** (a): Me_2SO_4, H_2O, NaOH, r.t., 4 h; for **2a**-d_6 (a): $(CD_3)_2SO_4$, H_2O, NaOH, r.t., 4 h; for **2b** (a): $Br(CH_2)_4Br$, $(i\text{-}Pr)_2EtN$, toluene, 110 °C, 15 h; for **3a**,**b** (b): i) *n*-BuLi, Et_2O, r.t., 48 h; ii) DMF, –60 °C, 1 h; iii) MeOH, –20 °C, 3 h.

We first carried out Knoevenagel condensation of 8-dimethylaminonaphthalene-1-carbaldehyde (**3a**) with active methylene compounds at room temperature in ethanol. With acyclic malononitrile (MN), the expected vinyl compound **4** could be smoothly obtained. However, treatment of **3a** with cyclic active methylene compounds, such as 1,3-dimethylbarbituric acid (DMBA) or 1*H*-indene-1,3(2*H*)-dione (ID) led, not fully unexpectedly,[7a] to zwitterionic benzo[*d*,*e*]quinolinium derivatives **5** and **6** as only isolable products in excellent yields (Scheme 2). Compounds **5** and **6** could be formed from intermediate vinyl compounds by cyclization via a *tert*-amino effect. The cyclic vinyl substituent might facilitate the ring formation by efficient delocalization of the developing negative charge and forcing the nucleophilic and electrophilic centers closer to each other by steric buttressing.

Compounds **5** and **6** could be easily distinguished from the vinyl compounds, based on upfield NMR shifts of the α-CH group (Figure 4). The X-ray analysis of **5** unambiguously revealed that C^1–N bond formation (bond distance of 1.630 Å, see Figure 5) did occur. The Wallis group, in their excellent comprehensive study, provided X-ray evidences for through-space attractive *peri*-interactions between nucleophilic donor and electron-deficient acceptor atoms in naphthalenes.[11] Moreover, they also reported on the formation of a naphthazepine from β-benzoyl-β-nitrovinyl analogue of **4** by heating a sample in an NMR tube, although the product was not isolated;[11a] interestingly, the synthetic value of the isomerization has not been explored.

We particularly focused on the possible transformations of compounds **4**–**6** to obtain novel series of 1,2-dihydronaphtho[1,8-*b*,*c*]azepines. Reactions were carried out in DMSO, neat, at different temperatures with traditional and microwave heating. From vinyl derivative **4**, azepine



Scheme 2 *Reagents and conditions*: for **4**: MN, EtOH, piperidine, r.t., 7 h; for **5**: DMBA, EtOH, piperidine, r.t., 5 h; for **6**: ID, EtOH, piperidine, r.t., 6 h.

Table 1 Effect of Different Reaction Conditions on Ring Closure[a]

Reaction	Solvent	Yield (%)	Time (h)	Temp (°C)
4 → **7**	DMSO	85	23.5	60
4 → **7**	DMSO	81	2.5	100
4 → **7**	DMSO	81	0.2	100[b]
4 → **7**	neat	61	3	160
4 → **7**	neat	80	0.3	162[b]
5 → **8**	DMSO	0	24	60
5 → **8**	DMSO	81	5	100
5 → **8**	DMSO	80	0.7	100[b]
5 → **8**	neat	67	2	180
5 → **8**	neat	60	0.7	180[b]
6 → **9**	DMSO	85	15	80

[a] Conditions: 2 mmol/10 mL DMSO.
[b] Microwave assisted reactions at 105 W max. power.

7 could only be isolated in a fairly good yield (Table 1). To investigate whether the rearrangement reaction takes place intramolecularly, compound **4**-d_6, the hexadeuterated dimethyl analogue of **4** was prepared from amine **1** following the methods described above, except using $(CD_3)_2SO_4$ for dimethylation of the amino group. The

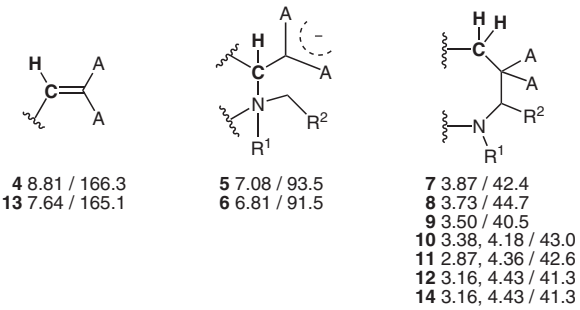


Figure 4 Some characteristic NMR data [^{1}H NMR, ^{13}C NMR in $CDCl_3$, δ (ppm)] of compounds **4**–**14**

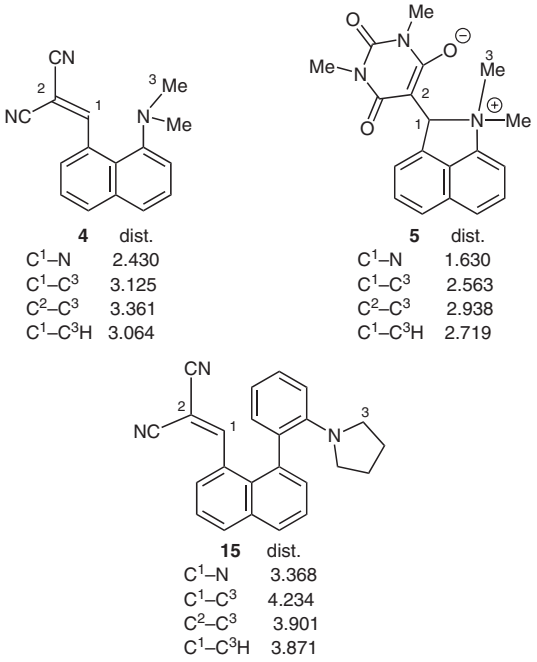
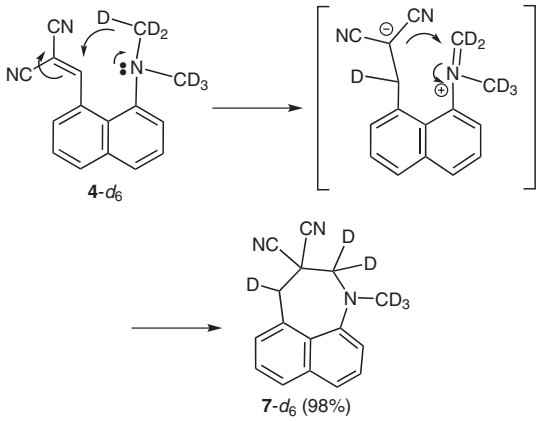


Figure 5 Characteristic atomic distances (Å) measured by X-ray diffraction

isomerization reactions of **4** and **4**-d_6 (Scheme 3) were monitored by ^{1}H NMR spectroscopy at 100 °C in DMSO-d_6 and the rate constants of reactions were calculated. The value of kinetic isotope effect (k_H/k_D = 2.5420/0.8920 = 2.85) supports that a hydrogen (or deuterium, respectively) located in the dimethyl group migrates in the rate limiting step. NMR and MS analyses of the product obtained from **4**-d_6 indicated that no deuterium loss occurred in the reaction (accordingly, it could be assigned to **7**-d_6), moreover, there could be detected no incorporation of deuterium when rearrangement of **4** to **7** was carried out in D_2O. On the basis of these findings, we propose that the isomerization of **4** affording azepine **7** proceeds in an intramolecular pathway. It could also be suggested that isomerization takes place in two steps, starting with a hydride transfer from the *N*-methyl group to the electron-deficient vinyl carbon affording a dipolar intermediate, following cyclization to azepine with the formation of a new C–C bond between the oppositely polarized carbon atoms in the second step. The short distances between at-

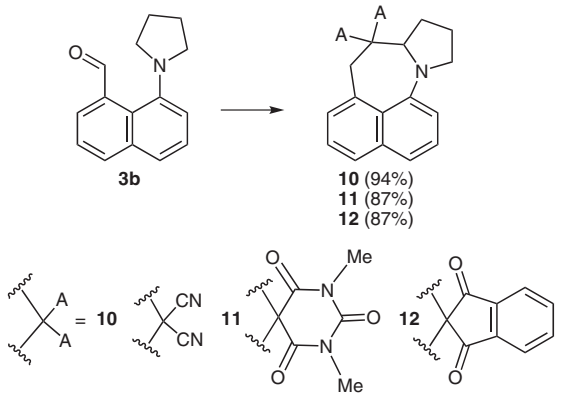
oms involved in the hydride transfer also support this mechanism (Figure 5).



Scheme 3 *Reagents and conditions*: for **7**-d_6: DMSO-d_6, 100 °C, 4 h.

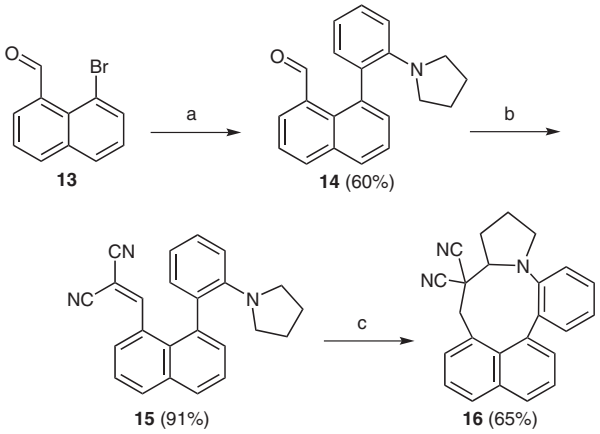
Transformation of zwitterionic compounds **5** and **6** to azepines **8** and **9**, respectively, could also be rationalized. It could occur through intermediate vinyl compounds formed with opening of the five-membered ring. When we monitored the rearrangement of **5** with ^{1}H NMR spectroscopy at temperatures 50–80 °C in DMSO-d_6, a broad signal was indeed identified that was assigned to a vinyl proton; upon elevating the temperature to 80 °C, there also appeared the signal set of naphthazepine **8**.

In the second series of reactions, 8-pyrrolidinonaphthalene-1-carbaldehyde (**3b**) was treated with active methylene compounds MN, DMBA, ID. Under mild conditions at room temperature, naphthazepines **10**–**12** could be isolated, that is, cyclization via type 2 *tert*-amino effect occurred. To achieve higher rates for formation of azepines **10**–**12**, reactions were carried out at 80 °C (Scheme 4). The increased reactivity of pyrrolidino vs. dimethylamino derivatives might be explained by more efficient overlap of nonbonding electron pair of pyrrolidine nitrogen with the aromatic π-system and a more favorable geometric position of the hydrogen for migration.



Scheme 4 *Reagents and conditions*: for **10**: malononitrile, piperidine, EtOH, 80 °C, 7 h; for **11**: 1,3-dimethylbarbituric acid, piperidine, EtOH, 80 °C, 4.5 h; for **12**: 1*H*-indene-1,3(2*H*)-dione, piperidine, EtOH, 80 °C, 3 h.

The scope of rearrangements was further investigated in system **D** (Figure 2) possessing a phenylnaphthyl skeleton with key groups positioned at the phenyl and naphthalene rings. Preparation of 8-(2-pyrrolidinophenyl)-1-vinylnaphthalene (**15**) was easily accomplished from 8-bromonaphthalene-1-carbaldehyde (**13**)[12] in three steps (Scheme 5). Suzuki cross-coupling reaction of **13** with *ortho*-pyrrolidinophenylboronic acid afforded **14**. The Knoevenagel condensation of **14** with MN led to vinyl derivative **15** in excellent yield. Interestingly, but not surprisingly, the X-ray analysis[13–16] of vinyl compound **15** showed that the distance between donor nitrogen and acceptor vinyl carbon was significantly longer than that in **4**, as a consequence of unfavorable steric effects (Figure 5). Upon heating of **15** in DMSO even at higher temperatures (microwave irradiation, 190 °C for 5 h), no cyclization was detected.



Scheme 5 *Reagents and conditions*: for **14**: 2-(pyrrolidin-1-yl)phenylboronic acid, $Pd[PPh_3]_4$, 0.2 M Na_2CO_3, DME, reflux, 1 h; for **15** malononitrile, piperidine, EtOH, r.t., 4 h; for **16**: [bmim]BF_4, 190 °C, 3 h.

Next, we thought to apply an ionic liquid as a particularly suitable solvent for high temperature polar reactions. The solution of **15** was heated in [bmim]BF_4 at 190 °C. Under these conditions the isomerization could indeed be achieved and pyrrolonaphtho[1,8-*e*,*f*]azonine **16**, representing a novel polycyclic ring system, was isolated in good yield (Scheme 5).[17]

In conclusion, novel 1,2-dihydrobenzo[*c*,*d*]indolium, naphtho[1,8-*b*,*c*]azepine and naphtho[1,8-*e*,*f*]azonine ring systems could be prepared from easily available *peri*-substituted naphthylamines by new extensions of *tert*-amino effect. Our results further demonstrate the high synthetic potential of *tert*-amino effect in the syntheses of otherwise hardly accessible medium-sized or larger fused aza-ring systems.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(16) The X-ray data are available from the Cambridge Crystallographic Data Centre CCDC under the numbers **5**: 7770044, **7**: 777045, **10**: 777046, **11**: 777047, **15**: 777048, respectively. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 (1223)336033 or e-mail: deposit@ccdc.cam.ac.uk. The details of the X-ray structures will be published elsewhere.
(17) Experimental data are available in Supporting Information.