Tetrahedron Letters 54 (2013) 5441–5444

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis and dynamic study of new *ortho*-(alkylchalcogen) acetanilide atropisomers. A second look at the hydrolysis of quaternary 2-methylbenzazol-3-ium salts

Susana S. Ramos [a], Lucinda V. Reis [b], Renato E. F. Boto [c], Paulo F. Santos [b], Paulo Almeida [c,*]

[a] UMTP and Department of Chemistry, University of Beira Interior, Rua Marquês d'Ávila e Bolama, 6200-001 Covilhã, Portugal
[b] Department of Chemistry and Centro de Química-Vila Real, University of Trás-os-Montes and Alto Douro, Apartado 1013, 5001-801 Vila Real, Portugal
[c] CICS–UBI, Health Sciences Research Center, University of Beira Interior, Av. Infante D. Henrique, 6200-506 Covilhã, Portugal

ARTICLE INFO

Article history:
Received 24 June 2013
Revised 19 July 2013
Accepted 23 July 2013
Available online 29 July 2013

Keywords:
Atropisomers
Dynamic NMR spectroscopy
VT NMR
Line shape simulation
Hydrolysis
2-Methylbenzazol-3-ium salts

ABSTRACT

The base-catalysed hydrolysis of *N*-ethyl-2-methylbenzazol-3-ium iodides was re-examined performing the reaction in boiling 96% ethanol, in the presence of triethylamine. The resulting unstable intermediates were isolated as the corresponding ether, thioether or selenoether derivatives, depending on the starting benzazole salt, by trapping via alkylation with ethyl and hexyl iodides, in moderate to good yields. Reduction of the *o*-(alkylchalcogen)acetanilides so obtained afforded the corresponding *o*-(alkylchalcogen)anilines. This methodology provides potential access to *o*-(alkylchalcogen)anilines bearing up to three different *N*-alkyl groups introduced in an unambiguous and regioselective way.

The *o*-(alkylchalcogen)acetanilides are axially chiral molecules due to restricted rotation around the N-aryl bond. The resulting atropisomerism has been studied using dynamic variable temperature NMR spectroscopy and the corresponding rotational barriers were determined for the first time in acetanilides bearing a single *ortho*-substituent other than the *tert*-butyl and iodine groups. The estimated free energy of activation of the interconversion of the rotamers ranged from 17.1 to 20.5 kcal/mol.

© 2013 Elsevier Ltd. All rights reserved.

In recent years, considerable research work has been carried out on the synthesis of cyanine dyes,[1] a well-known class of organic compounds with relatively good stability, high molar absorption coefficients, medium fluorescence intensities and narrow absorption bands. Furthermore, the wavelength of maximum absorption of these dyes can be tuned accurately from the near-UV to the near-IR by means of simple structural modifications. These unique photophysical and photochemical properties have turned cyanine dyes useful for numerous applications in many different areas.[1k] At present, a promising future for cyanine dyes is foreseen through the joint efforts of synthetic dye chemists, molecular biologists, physicists and medical scientists.

N-Alkyl-2-methylbenzazolium salts are common precursors in cyanine dye synthesis, and their ability to be substituted at the aromatic moiety and at the quaternary nitrogen atoms, is crucial for the structural diversity found in this family of dyes.[2]

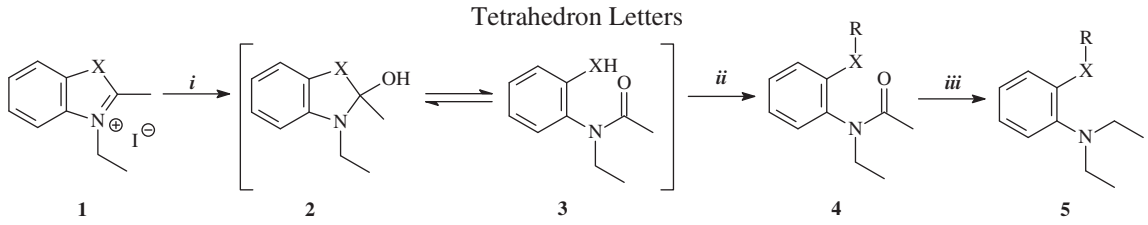
It has been observed that under basic conditions, as often used in cyanine dye synthesis, *N*-alkyl-2-methylbenzazolium salts interact with water, which turns the full understanding of this reaction important to avoid potential undesirable side reactions in cyanine dye preparation.[3d]

Herein we re-evaluated the base-catalysed hydrolysis of *N*-ethyl-2-methylbenzazol-3-ium salts **1** as a model, in the presence of residual water, resulting in the opening of the heterocyclic ring. The reaction does not stop at the *o*-hydrochalcogen intermediates **2**, as thought previously,[3] but subsequent cleavage of the heterocycle occurs and, under suitable alkylating conditions, the corresponding *o*-(alkylchalcogen)-*N*-ethylacetanilides **4** are obtained (Scheme 1).

Nevertheless some authors have previously mentioned the formation of ring opened products from the hydrolysis of 2-methylbenzothiazolium salts,[4] none was unequivocally isolated or deliberately trapped. The only ring opened product isolated and characterized was the disulfide dimer, generally obtained as the main reaction product, resulting from the oxidative coupling of two initially formed ring opened molecules. In such cases the hydrolysis was performed under rather more basic conditions than those used in our previous studies,[3] namely in aqueous sodium hydroxide[5a] or in piperidine in 96% ethanol.[6] A report where the action of a nucleophile on benzothiazolium salts led to an isolable species other than the corresponding disulfides, involved the reaction with sodium ethoxide, which afforded the alkoxybenzothiazole unopened product.[4b] To the best of our knowledge, only two examples of aromatic thioethers produced by the hydrolysis of benzothiazolium salts can be found in the literature, resulting from

* Corresponding author. Tel.: +351 275329174; fax: +351 275319056.
E-mail address: paulo.almeida@ubi.pt (P. Almeida).

0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.07.123



a: X = O, R = Et; **b**: X = O, R = Hex; **c**: X= S, R = Et; **d**: X = S, R = Hex; **e**: X = Se, R = Et

Scheme 1. Reagents and conditions: (i) NEt_3, 96% EtOH, reflux; (ii) EtOH, NaOH, RI, reflux; (iii) $LiAlH_4/AlCl_3$ (1/1), Et_2O, 0 °C to rt.

Table 1
Reaction times and yields of the synthesis of acetanilides **4** and anilines **5**

Compound	Reaction time[a] (h)	Yield[b] (%)	Compound	Reaction time (h)	Yield[b] (%)
4a	4.0	79	**5a**	1.5	87
4b	7.0	68	**5b**	2.0	84
4c	3.5	87	**5c**	1.5	92
4d	6.5	75	**5d**	2.0	88
4e	3.5	83	**5e**	1.5	93

[a] Overall.
[b] Isolated yield.

the trapping of the transient *o*-thiophenol by inter-[7a] and intramolecular[7b] alkylation of the thiol group, under strongly basic conditions.

Recently, it was described that under basic catalysis the effective intermediates from the hydroxylation of 2-methylbenzoxazolium and 2-methylbenzothiazolium iodides are the ring opened products, an evidence which was corroborated by ^1H and ^{13}C NMR data obtained by 600 MHz NMR.[5a] In that study 2-hydroxyacetanilide and a disulfide dimer resulting from the hydrolysis of 2-methylbenzoxazolium and 2-methylbenzothiazolium iodides, respectively, were unequivocally isolated and characterized. It was suggested[5] that the structures of several compounds arising from the hydrolysis of benzazoles reported by our group[3] should be revised.

As part of our efforts to definitively clarify this subject, we ended with an efficient and simple way to obtain asymmetrically substituted *o*-(alkylchalcogen)anilines **5** (Scheme 1). Thus, the hydrolysis of 3-ethyl-2-methylbenzazol-3-ium iodides **1**, readily accessible as previously described,[8] was carried out in boiling 96% ethanol, in the presence of triethylamine. The intermediate *N*-ethyl-(2-hydrochalcogen)acetanilides **3**, resulting from the cleavage of the 2-hydroxyazole moiety of the initially formed intermediate **2**, were alkylated in situ, to afford the corresponding (2-alkylchalcogen)-*N*-ethylacetanilides **4**, in moderate to good yields[9] (Table 1).

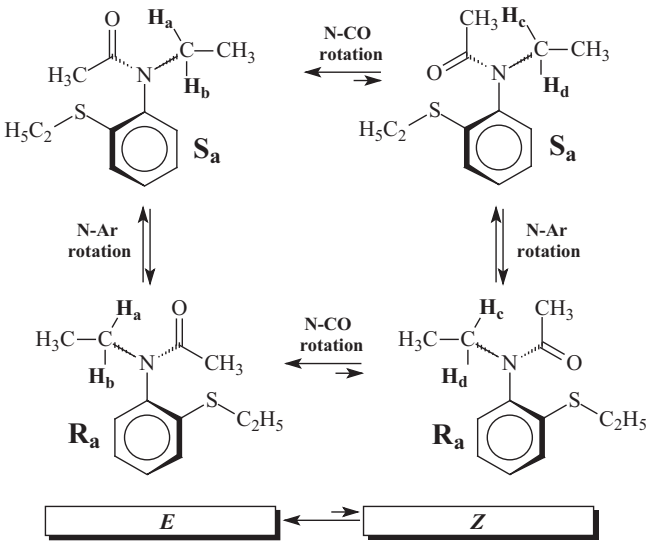
The alkylation step was used to trap the sulfur and the selenium open intermediates **3**, as well as the oxygen analogues, following a previously described strategy.[7] Subsequently, acetanilides **4** so obtained were converted to the corresponding 2-(alkylchalcogen)-*N*,*N*-diethylanilines **5** by reduction with lithium aluminium hydride in the presence of aluminium chloride.[10] The short overall reaction time, together with the mild conditions used and the good yields obtained, yet non optimized, make this reaction synthetically useful. All the obtained compounds showed spectral data, including high-resolution mass spectra, fully consistent with the assigned structures.

Acetanilides **4** were found to behave as enantiomeric atropisomers at room temperature due to restricted rotation around the N-aryl bond, responsible for the achiral properties. The word atropisomer is derived from the greek *a,* meaning *not*, and *tropos*, meaning *turn*, videlicet without rotation. This feature has been noticed in anilides bearing two *ortho*-groups, possessing very high rotational barriers, typically from <20 to ~30 kcal/mol,[11] and in anilides possessing a single bulky *ortho*-substituent, usually iodine or a *tert*-butyl group, showing rotational barriers of <20 kcal/mol.[12] Atropisomerism was also observed in *o*-hydrochalcogen-substituted acetanilides, formed in the basic hydrolysis of *N*-ethyl-2-methylbenzoxazolium and -benzothiazolium iodides.[5b] In this case the authors could establish by NMR that, in solution, the open hydroxylated benzazole compounds consist of four mutually interchangeable species, resulting from hindered rotation around the N-aryl bond (atropisomers) and around the N–CO bond (*E*/*Z* diastereoisomers). The later conformational isomerism is well known for amides due to the partial double bond character of the N–CO bond.[13] The *E* conformer was confirmed to be the major diastereoisomer.

In general, atropisomerism is recognized in solution by the non-equivalence of individual protons (namely CH_2 and CH_3 groups) in the ^1H NMR spectra.[5b,14] In particular, for acetanilides possessing at least one bulky *ortho*-substituent[11b,c,15] the restricted rotation around the N-aryl bond is responsible for the non-equivalence of the diastereotopic methylene protons, a typical sign of the existence of non-biaryl atropisomerism.

The ^1H NMR spectra of acetanilides **4**, at room temperature, are also consistent with the existence of four different interconvertible isomers in equilibrium such as depicted for **4c**, as a representative example, in Scheme 2.

Evidence of slow rotation about the N-aryl bond is immediately noticeable in the ^1H NMR spectrum of acetanilides **4** by the appearance of two pairs of equally intense signals (partially overlapped



Scheme 2. Enantiomeric and diastereoisomeric forms of acetanilide **4c** resulting from rotation around the N-aryl and N–CO bonds, respectively.

double quartets) generated by the geminal non-equivalent *N*-methylene protons (Fig. 1), in accordance with the literature.[5b] Considering the chemical shift difference between the non-equivalent methylene protons of each diastereoisomeric form it is apparent that the methylene protons of the *E*-conformation experience considerably more different magnetic local environments than those of the *Z*-conformation (Fig. 1). The *E*/*Z* ratio for all acetanilides **4** was found to be $\geqslant$96/4.

The conformational dynamic process of the *E* diastereoisomeric form of acetanilides **4** was investigated by variable temperature NMR (VT NMR) spectroscopy[16] and the corresponding rotational barriers were determined. This seems to be the first time that rotational barriers are determined for acetanilides bearing an alkylchalcogen group as *ortho*-substituent.

As an illustrative example, by increasing the temperature of a DMSO-d_6 solution of **4a**, the two partially overlapped double quartets of methylene protons H_a and H_b, at 3.63 and 3.43 ppm, respectively, came together yielding a very broad signal at 3.60 ppm, owing to the rapid interconversion of the two conformers at higher temperature (Fig. 2). The corresponding rotational barrier was determined by computer line shape simulation performed at different temperatures, yielding a series of rate constants for the exchange process. From that, an activation energy of 18.1 ± 0.2 kcal/mol for the free interconversion between the two conformers could be obtained using the Eyring equation.[17] The free energies of activation for the interconversion of the rotamers of **4b**–**e** were similarly determined and found to range from 17.1 to 20.5 kcal/mol (Table 2), being in accordance with the values disclosed in the literature for anilides possessing a single bulky *ortho*-substituent.[11b,c,12]

Coalescence temperature can be defined as the temperature at which the appearance of the NMR spectrum changes from that of two separate peaks to that of a single, flat-topped peak. At this temperature, both atropisomers have sufficient thermal energy to overcome the N-aryl bond rotational barrier and, therefore, free rotation occurs. Contrary to acetanilides **4a**,**b**, the coalescence temperature could not be ascertained for acetanilides **4c**–**e** due to the limitation of the spectrometer's working temperature to 413.15 K, preventing, consequently, the determination of rate constants above that temperature. However, the line shape simulations for **4c**–**e** provided a set of rate constants which was sufficient to allow the accurate calculation of the activation energy. In fact, the linear regression analysis performed for each compound **4a**–**e** was obtained from a set of eight to eleven data points, with correlation coefficients between 0.9873 and 0.9918, showing consistently a very high degree of linearity for the data obtained.

From the observation of Table 2, it is apparent that the estimated free energy of activation increases with the size of the chalcogen atom and decreases with the length of the alkyl group connected to it. Even though the first correlation may be easily rationalized based on the increase of the bulkiness of the chalcogen atom in the *ortho*-position ($\Delta G^{\ddagger}$: Se > S > O), other features besides steric hindrance must be involved to explain the opposite effect originated by the length of the alkyl group ($\Delta G^{\ddagger}$: Et > Hex) on the restriction of rotation around the N-aryl bond. On the other hand, T_c increases both with the size of the chalcogen atom and the length of the alkyl group.

In conclusion, the synthesis of some new *o*-(alkylchalcogen)acetanilides **4**, resulting from the base-catalysed hydrolysis of 3-ethyl-2-methylbenzazol-3-ium iodides, is presented as a regioselective, efficient and expeditious synthetic route to *o*-(alkylchalcogen)anilines **5**. This methodology provides potential access to *o*-(alkylchalcogen)anilines bearing up to three different *N*-alkyl groups introduced in an unambiguous and regioselective way.

The ring opened products resulting from the hydrolysis of *N*-alkyl-2-methylbenzazolium salts were unequivocally trapped and isolated as the ether, thioether and selenoether derivatives, in the form of the *ortho*-substituted acetanilides **4** and the *ortho*-substituted anilines **5**. Herein we revise the structures presented previously by us concerning *N*-alkyl-2-hydroxy-2-methylbenzazoles[3b] and heptamethinecyanines resulting from the nucleophilic

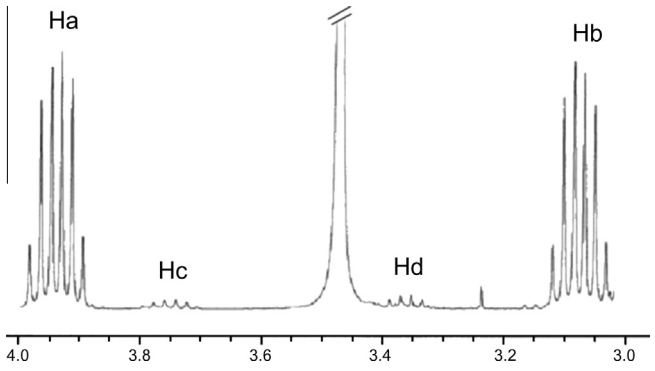


Figure 1. NMR signals of the non-equivalent geminal methylene protons of the *E* (H_a e H_b) and *Z* (H_c e H_d) diastereoisomeric forms of acetanilide **4c**.

Table 2
Interconversion energy barriers ($\Delta G^{\ddagger}$) and coalescence temperatures (T_c) for compounds **4**

Compound	$\Delta G^{\ddagger}$ (kcal/mol)	T_c (K)
4a	18.1 ± 0.2	388.15 ± 2
4b	17.1 ± 0.2	393.15 ± 2
4c	18.3 ± 0.2	>413.15
4d	17.8 ± 0.2	>413.15
4e	20.5 ± 0.2	>413.15

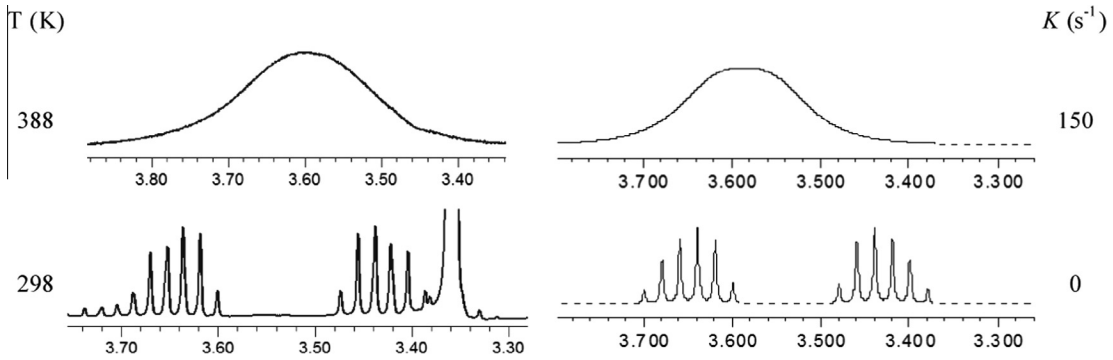


Figure 2. Left: temperature dependence of the ^{1}H NMR (400 MHz) signals of non-equivalent *N*-methylene protons of **4a** in DMSO-d_6. Right: computer line shape simulation from the rate constants obtained for same compound.

addition of the latter[3a,c,d] and correct them, respectively, to the isomeric *N*-alkyl-*o*-hydroxy-, *o*-sulfanyl- and *o*-selenylacetanilides and to the substituted heptamethinecyanines resulting from the nucleophilic addition of the latter two.

Finally, the atropisomerism of acetanilides **4** was studied using dynamic NMR spectroscopy and the corresponding rotational barriers were determined for the first time in acetanilides bearing a single *o*-alkylchalcogen substituent. Further studies involving the synthesis and VT NMR studies of new *o*-(alkylchalcogen)acetanilides substituted with *N*-alkyl groups other than ethyl and/or possessing a second group in the other ortho-position, along with the assessment of their biological properties are currently being undertaken, the results of which will be reported elsewhere.

Acknowledgments

This work was financed by FCT (Project PTDC/QUI-QUI/100896/2008) and COMPETE (Project Pest-C/SAU/UI0709/2011).

References and notes

1. (a) Reichardt, C. *J. Phys. Org. Chem.* **1995**, *8*, 761–773; (b) Rivière, F.; Romanenko, V. D.; Mazières, M. R.; Sanchez, M.; Wolf, J. G. *Tetrahedron Lett.* **1996**, *37*, 6717–6720; (c) Mishra, A.; Behera, R. K.; Behera, P. K.; Mishra, B. K.; Behera, G. B. *Chem. Rev.* **2000**, *100*, 1973–2012; (d) Voitenko, Z.; Mazières, M. R.; Sanchez, M.; Wolf, J. G. *Tetrahedron* **2001**, *57*, 1059–1066; (e) Abed El-Aal, R. M.; Koraiem, A. I. M. *Dyes Pigm.* **2002**, *54*, 121–129; (f) Mazières, M. R.; Duprat, C.; Bellan, J.; Wolf, J. G. *Dyes Pigm.* **2007**, *74*, 404–409; (g) Mojzych, M.; Henary, M. *Top. Heterocycl. Chem.* **2008**, *14*, 1–9; (h) Lopalco, M.; Koini, E. N.; Cho, J. K.; Bradley, M. *Org. Biomol. Chem.* **2009**, *7*, 856–859; (i) Mehranpour, A. M.; Hashemnia, S.; Maghamifar, R. *Synth. Commun.* **2010**, *40*, 3594–3602; (j) Su, J.-J.; Wang, L.-Y.; Zhang, X.-H.; Fu, Y.-L.; Huang, Y.; Wei, Y.-S. *J. Braz. Chem. Soc.* **2011**, *22*, 73–79; (k) Panigrahi, M.; Dash, S.; Patel, S.; Mishra, B. K. *Tetrahedron* **2012**, *68*, 781–805.
2. (a) Tyutulkov, N.; Fabian, J.; Mehlhorn, A.; Dietz, D.; Tadjer, A. *Polymethine Dyes: Structure and Properties*; St. Kliment Ohridsky University Press: Sofia, 1991; (b) Bach, G.; Daehne, S. Cyanine Dyes and Related Compounds. In *Rodd's Chemistry of Carbon Compounds*; Elsevier Science, 1997; pp 383–481. Chapter 15, Vol. IVb; (c) Miltsov, S.; Encinas, C.; Alonso, J. *Tetrahedron Lett.* **2001**, *42*, 6129–6131; (d) Encinas, C.; Miltsov, S.; Otazo, E.; Rivera, L.; Puyol, M.; Alonso, J. *Dyes Pigm.* **2006**, *71*, 28–36.
3. (a) Ramos, S.; Santos, P. F.; Reis, L. V.; Almeida, P. *Dyes Pigm.* **2002**, *53*, 143–152; (b) Santos, R.; Fernandes, L. M.; Boto, R. F.; Almeida, P. *Tetrahedron Lett.* **2006**, *47*, 6723–6725; (c) Nunes, M. J.; Reis, L. V.; Santos, P. F.; Almeida, P. *Tetrahedron Lett.* **2007**, *48*, 5137–5142; (d) Pais, I. R.; Nunes, M. J.; Reis, L. V.; Santos, P. F.; Almeida, P. *Dyes Pigm.* **2008**, *77*, 48–52.
4. (a) Clark, L. M. *J. Chem. Soc.* **1925**, *127*, 973; (b) Metzger, J.; Larivé, H.; Dennilauler, R.; Baralle, R.; Gaurat, C. B. *Soc. Chim. Fr.* **1964**, *11*, 2868–2878.
5. (a) Rashkova, J.; Tzvetkova, P.; Simova, S.; Viteva, L.; Gospodova, T. *Dyes Pigm.* **2009**, *82*, 360–364; (b) Viteva, L.; Gospodova, T.; Rahkova, J.; Abrahams, I.; Timtcheva, I.; Simova, S.; Mazieres, M. R.; Wolf, J. G. *Eur. J. Org. Chem.* **2007**, 3102–3114.
6. Babudri, F.; Bartoli, G.; Ciminale, F.; Florio, S.; Ingrosso, G. *Tetrahedron Lett.* **1984**, *19*, 2047–2050.
7. (a) Garmaise, D. L.; Paris, G. Y.; Komlossy, J.; Chambers, C. H.; McCrae, R. C. *J. Med. Chem.* **1969**, *12*, 30–36; (b) Federsel, H.-J.; Glasare, G.; Högström, C.; Wiestål, J.; Zinco, B.; Ödman, C. *J. Org. Chem.* **1995**, *60*, 2597–2606.
8. Pardal, A. C.; Ramos, S. S.; Santos, P. F.; Reis, L. V.; Almeida, P. *Molecules* **2002**, *7*, 320–330.
9. *General procedure for the hydrolysis of 3-alkyl-2-methylbenzazol-3-ium iodides* ***1***: A solution of the 3-alkyl-2-methylbenzazolium iodide **1** (1.0 mmol) and triethylamine (1.1 mmol) in 96% ethanol (100 mL) was heated under reflux. After the reaction was complete (30–60 min), the solvent was removed under reduced pressure and the crude reaction product was dissolved in EtOH. Following the addition of sodium hydroxide (1.2 mmol with reference to salt **1**) and the appropriate alkyl iodide (1.0 mmol with reference to salt **1**), the reaction mixture was heated under reflux for an additional 2–6 h. After completion of the reaction, the solvent was removed under reduced pressure, the crude residue was dissolved in CH_2Cl_2 and extracted sequentially with 10% aqueous HCl and 10% aqueous NaOH. The organic layer was then washed with water, dried over anhydrous Na_2SO_4 and evaporated to dryness. The resulting pinky-red oil was purified by column chromatography using CH_2Cl_2/MeOH (from 10/0 to 9/1) as the eluent. The pure brown-yellowish products were obtained in moderate to good yields (Table 1). Selected data. *N-Ethyl-N-[(2-(hexylthio)phenyl)]acetamide (**4d**)*: IR (ν_{max}/cm^{-1}): 2954, 2928, 2857, 1658 (C=O), 1583, 1470, 1392, 1297, 759, 734. ^{1}H NMR (400 Hz, DMSO-d_6): δ = 7.36–7.37 (m, 2H), 7.22–7.23 (m, 2H), 3.94 (dq, 1H, J = 13.8, 7.0 Hz), 3.09 (dq, 1H, J = 13.8, 7.0 Hz), 2.98 (q, 2H, J = 7.3 Hz), 1.62 (s, 3H), 1.56–1.62 (m, 2H), 1.36–1.43 (m, 2H), 1.23–1.27 (m, 4H), 1.00 (t, 3H, J = 7.1 Hz), 0.84 (t, 3H, J = 7.1 Hz) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.2, 139.6, 137.5, 130.3, 129.3, 126.6, 125.9, 41.9, 31.2, 30.5, 28.6, 28.4, 22.5, 22.4, 14.3, 13.4 ppm. HRMS (ESI-TOF) m/z 280.17216 (280.17351 calcd for $C_{16}H_{26}NSO$, $[M+H]^+$).
10. *General procedure for the reduction of acetanilides* ***4***: Finely powdered $AlCl_3$ (2.66 g, 0.02 mol) was added to a stirred suspension of $LiAlH_4$ (760 mg, 0.02 mol) in anhydrous Et_2O (50 mL), cooled in an ice-bath. To this mixture was added a solution of **4** (0.01 mol) in anhydrous Et_2O (100 mL) over a 30 min. period. After the mixture was stirred at room temperature for 1.5–2.0 h, it was cooled in an ice-bath, the excess of reducing agent was decomposed by the carefully addition of ethyl acetate and then a saturated aqueous Rochelle's salt solution was added and the mixture vigorously stirred for 30 min. The organic layer was separated and the aqueous phase was extracted with Et_2O. The combined organic layers were washed with water, dried over anhydrous Na_2SO_4, and the solvent evaporated under reduced pressure. Selected data. *N,N-Diethyl-2-(hexylthio)aniline (**5d**)*: Brownish oil. IR (ν_{max}/cm^{-1}): 2962, 2927, 2855, 1578, 1468, 1377, 757, 731. ^{1}H NMR (400 Hz, DMSO-d_6): δ = 7.15-7.17 (m, 1H), 7.04–7.09 (m, 3H), 2.96 (q, 4H, J = 7.1 Hz), 2.83 (t, 2H, J = 7.2 Hz), 1.58 (qt, 2H, J = 7.3 Hz), 1.36–1.43 (m, 2H), 1.27–1.28 (m, 4H), 0.91 (t, 6H, J = 7.1 Hz), 0.86 (t, 3H, J = 6.6 Hz) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 147.4, 135.9, 125.4, 124.4, 124.3, 122.6, 46.5 (2×), 30.7, 29.9, 28.0 (2×), 21.9, 13.8, 12.1 (2×) ppm. HRMS (ESI-TOF) m/z 266.19422 (266.19425 calcd for $C_{16}H_{28}NS$, $[M+H]^+$).
11. Representative examples: (a) Price, B. J.; Eggleston, J. A.; Sutherland, I. O. *J. Chem. Soc. (B)* **1967**, 922–925; (b) Shvo, Y.; Taylor, E. C.; Mislow, K.; Raban, M. *J. Am. Chem. Soc.* **1967**, *89*, 4910–4917; (c) Siddall, T. H.; Stewart, W. E., III *J. Phys. Chem.* **1969**, *73*, 40–45; (d) Oki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*; Deerfield Beach. FL: VCH, 1985. pp 160–193; (e) Curran, D. P.; Liu, W. D.; Chen, C. H.-T. *J. Am. Chem. Soc.* **1999**, *121*, 11012–11013; (f) Curran, D. P.; Chen, C. H.-T.; Geib, S. J.; Lapierre, A. J. B. *Tetrahedron* **2004**, *60*, 4413–4424; (g) Petit, M.; Geib, S. J.; Curran, D. P. *Tetrahedron* **2004**, *60*, 7543–7552; (h) Lapierre, A. J. B.; Geib, S. J.; Curran, D. P. *J. Am. Chem. Soc.* **2007**, *129*, 494–495. and references cited therein; (i) Yilmaz, E. M.; Dogan, I. *Tetrahedron: Asymmetry* **2008**, *19*, 2184–2191.
12. Representative examples: (a) Curran, D. P.; Qi, H.; Geib, S. J.; DeMello, N. C. *J. Am. Chem. Soc.* **1994**, *116*, 3131–3132; (b) Curran, D. P.; Hale, G. R.; Geib, S. J.; Balog, A.; Cass, Q. B.; Degani, A. L. G.; Hernandes, M. Z.; Freitas, L. C. G. *Tetrahedron: Asymmetry* **1997**, *8*, 3955–3975; (c) Clayden, J. *Angew. Chem., Int. Ed.* **1997**, *36*, 949–951; (d) Kondo, O. K.; Iida, T.; Fujita, H.; Suzuki, T.; Yamaguchi, K.; Murakami, Y. *Tetrahedron* **2000**, *56*, 8883–8891; (e) Ates, A.; Curran, D. P. *J. Am. Chem. Soc.* **2001**, *123*, 5130–5131; (f) Clayden, J. Ed. Tetrahedron Symposium-in-Print on Axially Chiral Amides. *Tetrahedron* **2004**, *60*, 4325-4558.; (g) Kitagawa, O.; Yoshikawa, M.; Tanabe, H.; Morita, T.; Takahashi, M.; Dobashi, Y.; Taguchi, T. *J. Am. Chem. Soc.* **2006**, *128*, 12923–12931.
13. Kim, Y.; Park, Y.; Park, K. *J. Mol. Struct.* **2006**, *783*, 61–65.
14. (a) Casarini, D.; Lunazzi, L.; Mazzanti, A. *J. Org. Chem.* **1997**, *62*, 3315–3323; (b) Clayden, J.; Moran, W. J.; Edwards, P. J.; LaPlante, S. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 6398–6401; (c) Díaz, J. E.; García, Ma. B.; Orelli, L. R. *J. Mol. Struct.* **2010**, *982*, 50–56; (d) Tabata, H.; Wada, N.; Takada, Y.; Oshitari, T.; Takahashi, H.; Natsugari, H. *J. Org. Chem.* **2011**, *76*, 5123–5131.
15. (a) Mills, W.; Kelham, R. *J. Chem. Soc.* **1937**, 274–278; (b) Kessler, H.; Rieker, A. *Liebigs Ann. Chem.* **1967**, *708*, 57–68; (c) Rodriguez, J.; Canoira, L.; Calderon, C.; Martinez-Ripoll, M.; Blanco, S. *J. Chem. Soc., Perkin Trans. 2* **1986**, 199–203; (d) Rodriguez, J.; Canoira, L.; Temporano, F. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1193–1196; (e) Rodriguez, J.; Canoira, L. *J. Chem. Soc., Perkin Trans.* **1994**, *2*, 1393–1396.
16. Variable-temperature spectra of **3** were obtained at 400 MHz. Temperature calibrations were performed before the experiments by means of a thermocouple whit an uncertainty not exceeding ± 2 K. The line shape simulations were performed by means of the gNMR software (Cherwell Scientific).
17. Eyring, H. *Chem. Rev.* **1935**, *17*, 65–77.