Tetrahedron Letters 57 (2016) 438–441

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Acid- and base-induced conformational alterations of *N*-aryl-*N*-troponyl amides

Ai Ito, Masanori Sato, Ryu Yamasaki, Iwao Okamoto *

Showa Pharmaceutical University, 3-3165, Higashi-Tamagawagakuen, Machida, Tokyo 194-8543, Japan

ARTICLE INFO

Article history:
Received 30 October 2015
Revised 25 November 2015
Accepted 9 December 2015
Available online 10 December 2015

Keywords:
Molecular switch
Aromatic amide
Tropolone
pH-dependent

ABSTRACT

We have investigated acid- and base-induced conformational alterations of *N*-aryl-*N*-troponyl amides containing an electron-donating group on the phenyl ring. NMR spectral studies indicated that the *E*/*Z* conformational preferences of these amides can be reversibly controlled by pH-dependent protonation or deprotonation of the tropolone moiety. Thus, these compounds have potential applications as acid/base-controllable molecular switches.

Molecular switches[1–3] can be used as triggers to modify the three-dimensional structure of macromolecules or supramolecules, and thereby to modulate their biological activity or functionality, and they have attracted much attention in such fields as nanotechnology, analytical chemistry, and chemical biology.[4–8] They can be operated by various external stimuli, such as electric current,[9–12] temperature,[13] pH,[14–18] or light.[19–21] One example of a molecular switch is the amide bond, which can take *cis* or *trans* conformation. Most secondary amides, such as benzanilide and acetanilide, favor *trans* form, but *N*-methylation of these amides causes conformational alteration from *trans* to *cis*.[22,23] In most cases, molecular switches have high energy barriers between the on and off states.[24–26] On the other hand, *cis*–*trans* conformational change of amide is an equilibrium reaction. Nevertheless, change of conformational ratio can be used to control functional activity: for example, Am 80 (*trans* amide form) exhibits potent retinoid activity, whereas *N*-methylation switches the preferred conformation to *cis* amide, which is inactive.[27,28]

One reason for the *cis* conformational preference associated with *N*-methylation is considered to be the effect of electronic repulsion between the carbonyl lone pair and the aryl π-electrons.[29] Therefore, we speculated that the conformational preference in *N*,*N*-diaryl type amides might be controlled by adjusting the relative π-electron densities of the two *N*-aromatic moieties. We have previously shown that some aromatic amides switch their conformation in response to external stimuli, such as pH and redox reaction.[30–32]

Tropolone, having a seven-membered ring, is a nonbenzenoid aromatic and its acidity (pK_a = 6.92) is intermediate between those of benzoic acid and phenol.[33] Its structure is of interest to synthetic and medicinal chemists, because several natural products bearing a tropolone moiety have potent antitumor, antibacterial, antifungal, antiviral and antimicrobial properties,[34–36] and it has been shown that tropolone can serve as a pharmacophore in place of benzoic acid or phenol.[37] We have been investigating the structural and medicinal chemistry of tropolone and its derivatives.[38,39] We focused on the fact that tropolone is amphoteric, that is, it works as both an acid and a base; it exists as a dihydroxytropylium cation in acidic solution and as a tropolonate anion in basic solution (Fig. 1).[40]

In order to examine the feasibility of using tropolones as molecular switches, in this study we synthesized various *N*,*N*-diaryl amides bearing tropolone and investigated their conformational preferences in solution by means of NMR measurements. Our results indicate that the conformational preferences of these amides depend on the relative π-electron densities of the two *N*-aromatic parts, and can be modified simply by protonation and deprotonation of the tropolone moiety.

To investigate the conformational preferences of *N*,*N*-diarylamide derivatives bearing tropolone, we designed and synthesized *O*-methyl troponyl amides **3a–c** and tropolonyl amides **4a–c** (Scheme 1). 5-Iodo-2-methoxytropone **1**[37,41] was coupled with aniline derivatives in the presence of Pd catalysts to afford **2a–c** in 75–91% yield, and these products were acetylated to give **3a–c**

* Corresponding author. Tel.: +81 42 721 1569; fax: +81 42 721 1570.
E-mail address: iokamoto@ac.shoyaku.ac.jp (I. Okamoto).

http://dx.doi.org/10.1016/j.tetlet.2015.12.048
0040-4039/

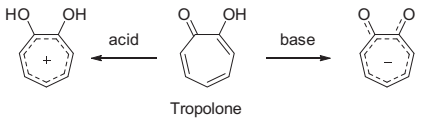
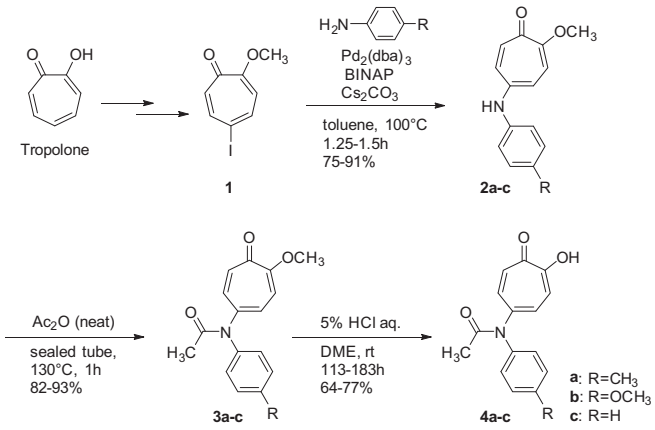


Figure 1. Protonated–neutral–deprotonated forms of tropolone.



Scheme 1. Synthesis of *N*-aryl-*N*-troponyl amides **3** and **4**.

in high yield. Tropolonyl amides **4a**–**c** were prepared by hydrolysis of **3a**–**c**, respectively.

In order to investigate the conformational preferences of **3a**–**c** and **4a**–**c** in solution, ^{1}H NMR spectra of these amides were measured (Fig. 2). The conformer ratios are summarized in Table 1. At 303 K, ^{1}H NMR spectra of **3a–c** and **4a–c** in CD_2Cl_2 showed a single set of signals. However, when the temperature was lowered to the range of 283–273 K, these signals became broadened, and finally two distinct sets of signals appeared (see Supplementary data). The major conformers of **3a–c** and **4a–c** are all *Z* form, with the *N*-phenyl group located opposite the amide oxygen atom. These assignments were confirmed by means of NOE experiments (see Supplementary data). In **3a–c** bearing 2-methoxytropone, the major *Z*-conformers exist at similar ratios: 73% (**3a** at 233 K), 74% (**3b** at 223 K) and 72% (**3c** at 203 K) (entries 1–3). Compounds **4a–c** bearing tropolone showed a similar tendency (*Z*-conformer ratio: 75–79%) (entries 4, 8 and 11).

We also measured the ^{1}H NMR spectra of **4a–c** in various solvents, such as DMF-d_7 and CD_3OD. Two conformers of **4a–c** were distinguished at low temperatures. Since NOE measurements of **4a–c** in DMF-d_7 and CD_3OD were not feasible due to the viscosity of the solutions, the chemical shifts of the two acetyl groups of **4a–c** in these solvents were compared at low temperature (see Supplementary data, Fig. S13). The major acetyl signals of **4a–c** in DMF-d_7 and CD_3OD were similar to those in CD_2Cl_2 in each case. The fact that the ratio of the acetyl peak of major conformer was

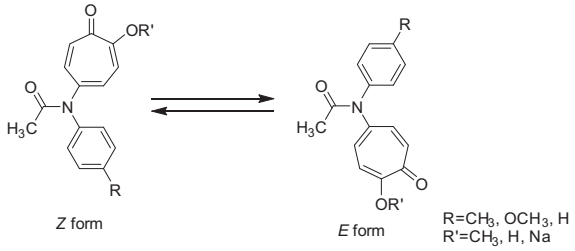


Figure 2. Conformational equilibrium of *N*-aryl-*N*-troponyl amides.

Table 1
Conformational preferences of **3a–c** and **4a–c** in various solutions

Entry	Amide[a]	*R*	*R*′	Solvent	Major ratio[b] (%)	Temp (K)	ΔG^{0c} (kcal/mol)
1	**3a**	CH_3	CH_3	CD_2Cl_2	*Z* 73	233	0.46
2	**3b**	OCH_3	CH_3	CD_2Cl_2	*Z* 74	223	0.46
3	**3c**	H	CH_3	CD_2Cl_2	*Z* 72	203	0.38
4	**4a**	CH_3	H	CD_2Cl_2	*Z* 77	243	0.58
5	**4a**	CH_3	H	CD_3OD	*Z* 78	243	0.61
6	**4a**	CH_3	H	DMF-d_7	*Z* 74	233	0.48
7	**4a**	CH_3	H	CD_3OD/ DMF-d_7 1:1	*Z* 74	243	0.50
8	**4b**	OCH_3	H	CD_2Cl_2	*Z* 79	243	0.64
9	**4b**	OCH_3	H	CD_3OD	*Z* 81	233	0.67
10	**4b**	OCH_3	H	DMF-d_7	*Z* 76	243	0.55
11	**4c**	H	H	CD_2Cl_2	*Z* 75	223	0.48
12	**4c**	H	H	CD_3OD	*Z* 75	253	0.55
13	**4c**	H	H	DMF-d_7	*Z* 70	233	0.47

[a] See Figure 2.
[b] The ratio was determined by ^{1}H NMR measurement.
[c] $\Delta G^0 = -RT \ln([E]/[Z])$.

not affected by changing the solvent ratio in DMF-d_7/CD_3OD = 1:1 indicated that the conformational alteration didn't happen. Therefore, these results indicate that the major conformers of **4a–c** in DMF-d_7 and CD_3OD are the *Z* form (70–81% ratio), as is the case in CD_2Cl_2 (entries 5, 6, 7, 9, 10, 12 and 13). Thus, **3a–c** and **4a–c** exist predominantly in *Z* form in CD_2Cl_2, DMF-d_7 and CD_3OD, and the *Z*-conformational preference of these amides depend on the relative π-electron densities of the two *N*-aromatic parts, in accordance with previous findings.[30,31]

In order to probe the pH-dependent conformational alteration of these amides **3** and **4**, the ^{1}H NMR spectra of **3** and **4** were measured under acidic and/or basic conditions. It is known that tropone and tropolone derivatives are stronger bases than most other unsaturated ketones due to the stability of the tropylium cation; for example, these compounds are completely protonated in 40% sulfuric acid.[42]

First, we focused on **1** and tropolone as simple models, and we measured their ^{1}H NMR spectra in the presence of acids, such as $HBF_4{\cdot}Et_2O$, and TFA-*d*. The addition of $HBF_4{\cdot}Et_2O$ (25 equiv) to **1** in $CDCl_3$ caused lower field shifts, and further addition of Et_3N (25 equiv) as a base restored the signals of **1** in $CDCl_3$ (see Supplementary data, Fig. S14). These signal changes can be considered as the result of protonation at the oxygen atom of **1**. In contrast, when $HBF_4{\cdot}Et_2O$ (25 equiv) was added to tropolone in $CDCl_3$, in addition to protonated species of tropolone, the signals of difluoroboron complex of tropolone appeared. These results indicated that $HBF_4{\cdot}Et_2O$ was not suitable for this study. Therefore, we used TFA-*d* as an acid instead of $HBF_4{\cdot}Et_2O$. Addition of a large excess of TFA-*d* (100 equiv) caused lower field shifts, and protonation of tropolone by TFA-*d* was observed, as in the case of **1** (see Supplementary data, Fig. S15).

Next, to check the deprotonation process, the ^{1}H NMR spectrum of sodium tropolonate was measured (see Supplementary data, Fig. S16). The chemical shifts of sodium tropolonate were observed at higher field compared to the δ value without base, owing to deprotonation. Next, we investigated the ^{1}H NMR spectra of **3a–c** and **4a–c** under acidic or basic conditions. The conformer ratios are shown in Table 2. In the case of **3a–c**, protonation with $HBF_4{\cdot}Et_2O$ caused lower field shifts of the aromatic proton signals, and two conformers of the protonated **3a–c** were observed at low temperature (see Supplementary data).

In the case of protonated **3a**, the major acetyl proton signal was clearly distinguishable from the minor acetyl proton signal, and the major conformer of protonated **3a** was readily assigned as the *Z*