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Investigations of the Halogen Dance Reaction on N-Substituted 2-Thiazolamines[§]

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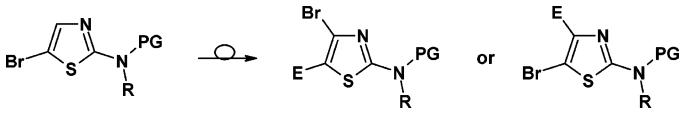

The halogen dance (HD) reaction on various 2-thiazolamine systems was investigated providing an easy access to a series of 5-substituted 4-bromo-2-thiazolamine derivatives. We could show that HD is a very favored process for the investigated systems and that prevention of HD is only possible when optimized reaction conditions and selected electrophiles are applied.

Introduction

Thiazoles bearing substituents in positions 4 and 5 are an upcoming class of compounds with interesting biological properties.[1] In a search for a versatile and facile method to prepare such compounds, the halogen dance (HD)[2] reaction promised to be a powerful strategy. HD reactions can be induced by various bases, e.g., $NaNH_2$, anilides, alkoxides, BuLi, or LDA,[2] and generalized in a way depicted in Scheme 1.

In the literature, such reaction types have been referred to by different names such as halogen scrambling, halogen migration, halogen isomerization, halogen dance (HD), or base-catalyzed halogen dance (BCHD) reactions. Since the first observation of a halogen dance (HD) reaction in 1953,[3] intensive research on both aromatic as well as heteroaromatic systems has been carried out. The heteroaromatic systems included thiophene[4] and benzo[*b*]thiophene,[5] furan,[2c] isothiazole,[6] imidazole,[7] pyrazole,[8] pyridine,[9] quinoline,[10] and imidazo[1,2-*a*]pyridine,[11] and very recently, Stangeland and Sammakia[12] reported the first HD on a thiazole derivative. This publication

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§ Dedicated to the memory of Prof. Roland Schmid.

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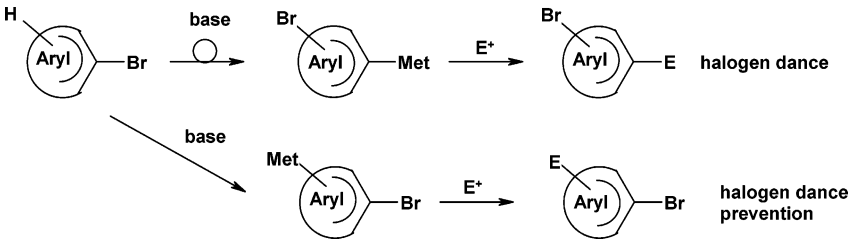
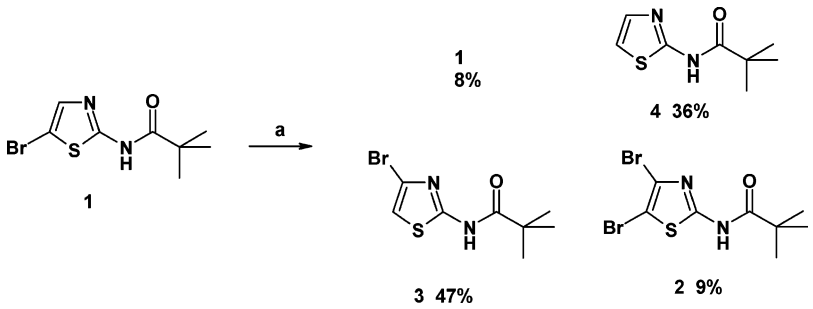
SCHEME 1. General Scheme of a HD



SCHEME 2. Product Distribution in the Initial Lithiation Experiment[a]



[a] Key: (a) (1) **1** added to LDA at −80 °C, 30 min at −20 °C; (2) 1,2-dibromoethane added at −40 °C.

TABLE 1. General Guidelines to Control HD Reactions

HD	HD prevention
low temperatures	high temperatures
no excess of base	excess of base
addition of base to the halide	addition of halide to the base
THF	THP
slow reacting electrophile	fast reacting electrophile

prompted us to report our results in this research field. In 2-substituted thiazoles, halogens can be transferred via HD from the 5-position into the by far less accessible 4-position of the thiazole moiety. While creating a new reactive center in the 4-position this approach offers the possibility to introduce also various electrophiles into the 5-position by quenching the intermediate. The bromine in the 4-position can be then also used for subsequent transformations, e.g., metal−halogen exchange followed by reaction with electrophiles as well as cross-coupling reactions leading finally to a variety of 2,4,5-trisubstituted thiazoles.

To obtain complete HD it is crucial that unlithiated starting material and already lithiated intermediates are present simultaneously in the reaction mixture in order to start a cascade of metal−halogen exchanges. Since these exchange reactions are equilibria, the product distribution found after quenching the reaction reflects the reaction progress at the moment of the quench. If one intermediate is considerably more stable than the others, one product can be formed predominantly or even exclusively. Extensive research has been carried out on various systems and general procedures have been developed to achieve complete HD or complete HD prevention which must of course be adapted and optimized for any particular synthetic problem.[2c] Some general guidelines providing useful hints for initial experiments are summarized in Table 1. Low temperatures favor HD since in that case the initial lithiation is slowed and the possibility of having unlithiated starting material together with an already lithiated species is increased. For the same reason, less than a stoichiometric amount of base should be used to enhance the HD reaction. The order of addition of substrates and reagents has also an influence on the course of the reaction as well as the solvent and the selected electrophile. THF as solvent, addition of base to the starting material, and slowly reacting electrophiles proved to favor HD reactions. Tetrahydropyran (THP) on the contrary often helps to prevent HD reactions since the initial lithiation is faster in this solvent compared to THF due to the increased reactivity of lithium organyls in THP (Table 1).[2c]

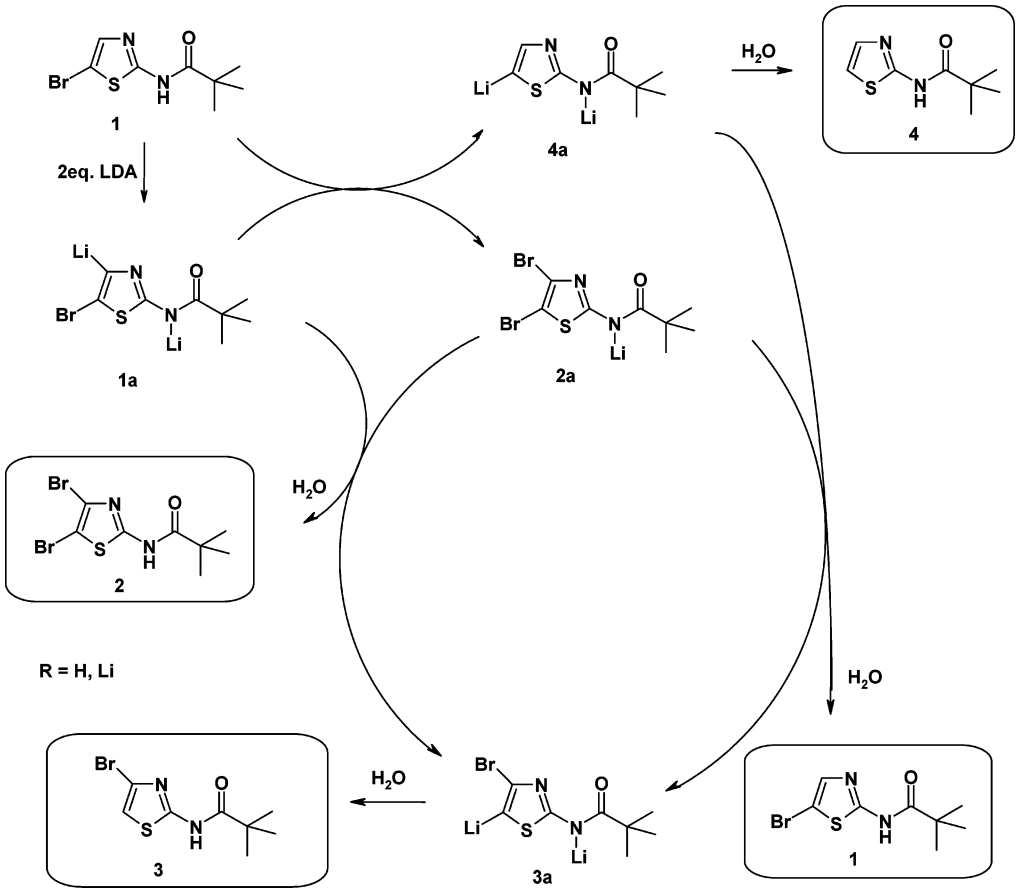
Results and Discussion

We first observed a HD during attempts to obtain *N*-(4,5-dibromothiazol-2-yl)-2,2-dimethylpropanamide (**2**) from *N*-(5-bromothiazol-2-yl)-2,2-dimethylpropanamide (**1**). Since direct bromination using various general methods[13] was not successful, we tried to introduce the bromine via lithiation with LDA (2.1 equiv) and subsequent quenching with 1,2-dibromoethane. After workup, a mixture of dibrominated, monobrominated, and nonbrominated products was isolated and separated (Scheme 2).

The desired product **2** was obtained in only 9% yield, and three other compounds were isolated. Besides the starting material **1** (8%), debrominated *N*-(thiazol-2-yl)-2,2-dimethylpropanamide (**4**) (36%) and *N*-(4-bromothiazol-2-yl)-2,2-dimethylpropanamide (**3**) (47%) as the major product were isolated. A hypothesis to explain the formation of all compounds would be a HD mechanism as depicted in Scheme 3. The first step in this reaction sequence is of course the lithiation of the starting material **1** to form the organometal species **1a**. Intermediate **1a** can by itself act as a lithiating agent and reacts with starting material **1** to give a metal−halogen ex-

(13) Applied bromination conditions: Br_2 in $CHCl_3$ at rt and reflux, Br_2 in AcOH at rt and reflux, Br_2 in AcOH/AcONa at rt and reflux.

SCHEME 3. Suggested Mechanism for the Observed HD on 1



change to form the intermediates **2a** and **4a**. This is the beginning of a cascade, where all the intermediates can interact with each other to form the species depicted in Scheme 3. Quenching the reaction with water could in general lead to all observed compounds since all the reactions are equilibria. The addition of 1,2-dibromoethane should further promote the HD since the 4,5-dibromo compound **2** can act as a co-catalyst. Co-catalysts in HD reactions are usually polyhalogenated species, which act as electrophilic halogen donors.[2c]

The reason a HD can occur on an aromatic system can be explained by differences in the acidity of the various positions which correlates with the different stability of the formed lithiated species.[14] In this particular case, the 5-position is more acidic than the 4-position, therefore favoring lithiation at position 5 relative to the 4-position.

Besides the possibility of obtaining the desired compound **2**, this sequence would also give access to a range of interesting 4-substituted and especially 4,5-disubstituted thiazoles which in particular are difficult to prepare via other routes.[6] Having this in mind, we tried to find reaction conditions whereafter the initial lithiation of the 4-position either quantitative HD or complete prevention of HD can be achieved.

Halogen Dance Conditions. To obtain complete HD, reaction conditions were applied, which—according to the literature[2c]—promote efficiently the rearrangement process (Table 1). Investigating the introduction of bromine via HD reaction as a model transformation in more detail we changed to bromine as superior electrophile compared to 1,2-dibromoethane (Table 2, entries 3 and 4).

TABLE 2. Introduction of Electrophiles into the 5-Position

entry	E	electrophile	product	yield (%)
1	CHO	DMF	**5a**	92
2	C_6H_{10}(OH)	cyclohexanone	**5b**	73
3	Br	Br_2	**2**	93
4	Br	1,2-dibromoethane	**2**	20
5	I	I_2	**5c**	76
6	PhCH(OH)	benzaldehyde	**5d**	86
7	TMS	TMSCl	**5e**	74
8	H	H_2O	**3**	99
9	$(C_6H_5)_2$COH	$(C_6H_5)_2CO$	**5f**	46

To find optimized HD conditions, the reaction to the 4,5-dibromo compound **2** starting from the 5-bromo compound **1** was investigated in more detail. Since we had the 5-bromo compound **1** and the 4-bromo compound **3** already in hand, we could follow the conversion from **1** to **3** in our lithiation experiments by TLC before adding bromine as electrophile. In our initial experiment, a solution of compound **1** in dry THF was treated dropwise with 2.1 equiv of LDA at −85 °C over a period of 15 min. Quenching with bromine gave a conversion to 80% of HD product **2** besides starting material **1**. By using a greater excess of base (3.3 equiv), full conversion to the HD product was observed. The method was simplified when we found that an "inverse" addition of base and low reaction temperatures (−80 °C) are not necessary in this case. Addition of the halide to the LDA solution at 0 °C

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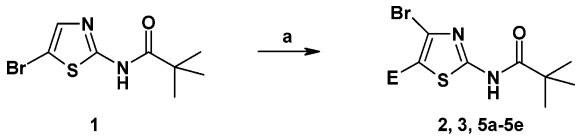
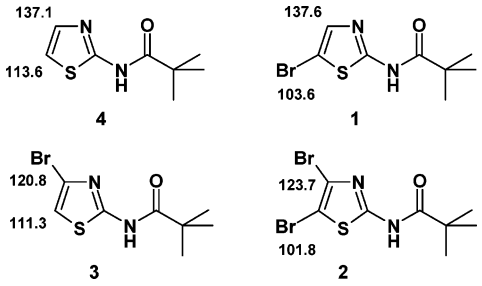
SCHEME 4. Introduction of Electrophiles into the 5-Position[a]



[a] Key: (a) (1) 3.3 equiv of LDA, 0 °C, 30 min, THF; (2) 3.3 equiv of E^+.

SCHEME 5. Characteristic ^{13}C-Shifts of the C-4 and C-5 in Various 2-Thiazolamine Derivatives



gave complete HD within minutes. We believe that a complete HD under such conditions occurs due to the great difference in the acidities of the 4- and 5-position of the thiazole system.[14] Although this finding simplified the experimental procedure, it also suggested that prevention of the HD could be expected to be rather difficult.

With a convenient methodology for complete HD in our hands, 4-bromo-5-lithiated intermediate **3a** was trapped with various electrophiles and several substituents were introduced into the 5-position in good to excellent yields (46−99%; Table 2, Scheme 4).

An easy confirmation that HD occurred was obtained by analysis of the ^{13}C spectra of the various products. In *N*-(thiazol-2-yl)-2,2-dimethylpropanamide **4**,[15] the thiazole carbons 4 and 5 show δ values of 137.1 ppm (C-4) and 113.6 ppm (C-5), respectively. Bromination of the 5-position leads to a shielding of the C-5 carbon to 103.6 ppm due to the heavy atom effect of the bromine whereby the C-4 carbon shift is almost unaffected with a value of 137.6 ppm (Scheme 5). On the other hand, in the 4-brominated compound **3** the C-5 carbon at 111.3 ppm is almost unaffected compared to the unbrominated compound **4**, whereby the C-4 carbon due to the heavy atom effect is shifted again to 120.8 ppm. Very similar effects were found for all investigated HD products making it easy to determine if a HD or a HD-prevention product was formed. Additionally the structure of **5d** was confirmed by X-ray analysis (Supporting Information). The carbon shift for C-4 is in good agreement with the above-specified characteristic range (118.8 ppm).

Prevention Conditions. The much more difficult task was to find reaction conditions to prevent the HD enabling the introduction of electrophiles into the 4-position of 5-bromo-*N*-(thiazol-2-yl)-2,2-dimethylpropanamide **1**. To prevent the HD reaction it is necessary that no unlithiated starting material is present next to the initially lithiated species, hence, not allowing a metal−halogen exchange which would start a cascade leading to HD products. This means that the initial lithiation should be a fast process, which can be ensured in many cases by using elevated temperatures and slow addition of the halide to an excess of base (Table 1). The use of a fast reacting electrophile also helps to obtain HD-prevention products: for that purpose we chose TMSCl. Since in dry THF the HD reaction took place also under reaction conditions, which according to the literature,[2c] should prevent the HD we switched to dry THP since it is described as a solvent where HD-prevention is sometimes favored. Although various temperatures and amounts of base (2.1−4.3 equiv) were applied, no HD-prevention products were obtained. In all cases the halide was added very slowly (up to 45 min/mL) to an excess of base at temperatures ranging from −110 °C (THP/hexane) to 0 °C (THP). Consequently, the HD-reaction seems to take place immediately after the lithiation.

Influence of the NH Proton. Since attempts to prevent the HD were not successful so far, we investigated if the NH proton has a significant influence on the HD reaction. Slow deprotonation at this position would favor HD reactions because already formed 4-lithio species could be intermolecularly reprotonated. This leads to mixtures of lithiated and unlithiated species, which could be a reason HD prevention was not successful so far. Therefore proton donation by the amide nitrogen atom should be prevented and we had in mind to methylate the amide nitrogen. We found that deprotonation with NaH or LDA (1.05−1.20 equiv) and subsequent quenching with MeI or DMS (2.0−14 equiv) led to methylation of the ring nitrogen (compound **6**) and not to the desired methylation of the amide nitrogen (Scheme 6, optimized conditions). The structure of **6** was confirmed by X-ray analysis (Supporting Information). Methylation on the ring nitrogen is not totally surprising since it is known in the literature[16] that the parent thiazole-2-amine exists in two tautomeric structures although the equilibrium lies well on the side of the amine species.

When LDA was used as base, methylation did not proceed to completion which suggests that LDA does not abstract the NH-proton very efficiently. Consequently, this effect might hinder the HD prevention, which is consistent with our results. To support this hypothesis other systems with completely substituted amide nitrogen in 2-position were synthesized.

Compound **7** was obtained via a straightforward synthesis (Scheme 7) according to the literature.[17] Initially, the pivaloyl group was used again as the protecting group for the amine functionality because of its stability under bromination conditions. During our first experiments, we observed that the pivaloyl group in *N*-phenyl-*N*-(thiazol-2-yl)-2,2-dimethylpropanamide **8** shows a great tendency to migrate into the 5-position of the thiazole ring under lithiation conditions even at low temperatures

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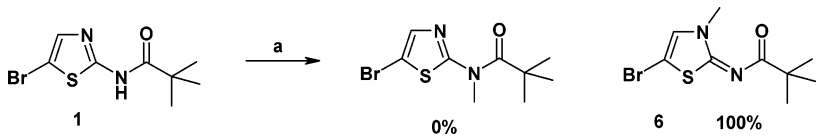
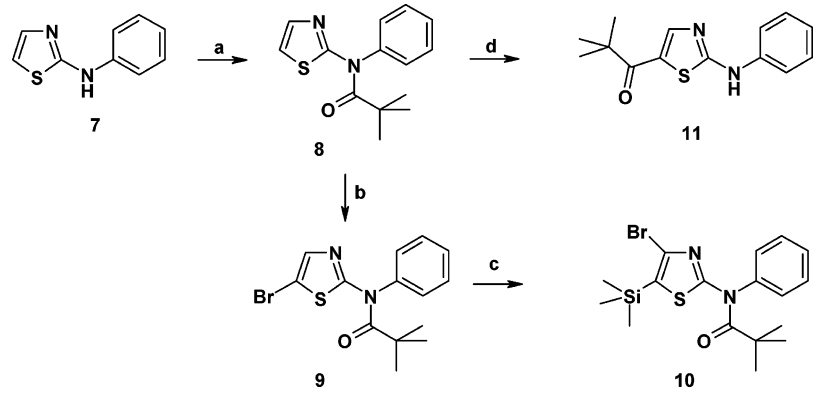
SCHEME 6. *N*-Methylation Experiment of 1[a]



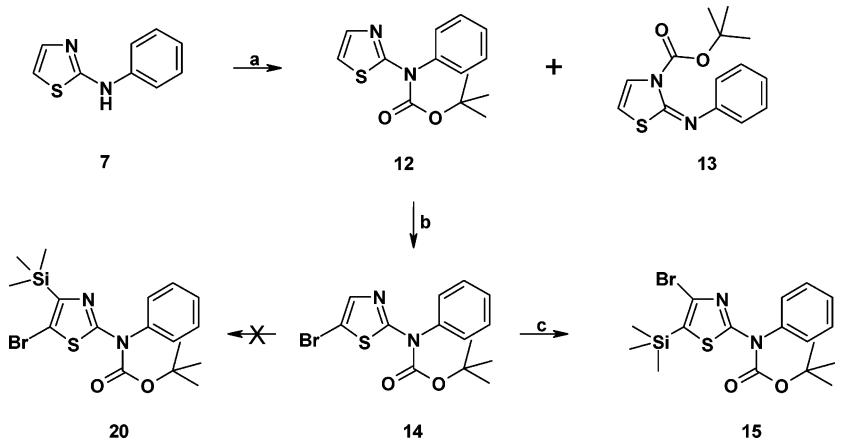
[a] Key: (a) (1) 1.2 equiv of LiH; (2) 1.5 equiv of DMS, 66 °C.

SCHEME 7. Synthesis and Lithiation Experiments of Compounds 8 and 9[a]



[a] Key: (a) NaH, pivaloyl chloride, THF, reflux; (b) Br_2, NEt_3, $CHCl_3$, rt; (c) LDA, TMSCl, THF, −100 °C; (d) LDA, THF, −100 °C to rt.

SCHEME 8. Synthesis and HD Experiments with 14[a]



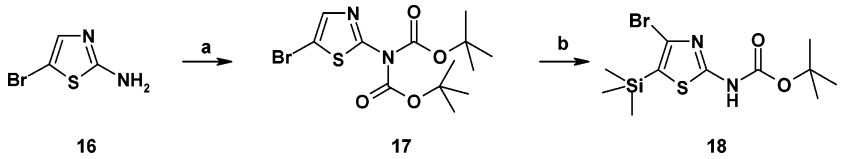
[a] Key: (a) DMAP, BOC-anhydride, THF, reflux; (b) Br_2, NEt_3, $CHCl_3$, rt; (c) LDA, TMSCl, THF, 0 °C.

(−80 °C) to form compound **11** (Scheme 7). This migration must be an intermolecular process since for sterical reasons an intramolecular migration is not possible. To our knowledge this is the first intermolecular migration of a pivaloyl group observed whereas intramolecular migrations have already been reported in the literature.[18] This observation suggested that 5-bromo compound **9** is also not a suitable substrate for HD-dance prevention reactions since again a migration of the protecting group has to be expected at higher temperatures. At temperatures below −80 °C (−110 to −90 °C) the HD product **10** (69%) was obtained but also at these low temperatures partial migration of the protecting group to form **11** was observed.

Consequently, we chose the BOC group as the protecting group since we knew from earlier research that the BOC group has a lower tendency to migrate under lithiation conditions.[19] Similar to our experience in the methylation, during the protection step of **1** the required major product **12** again was accompanied by 8% of the endocyclic protected compound **13**. As expected the BOC group was not as stable as the pivaloyl group under bromination conditions and partial loss of the protecting group during bromination could not be avoided. But still the desired product **14** was obtained in 53% yield. At low temperatures, the BOC group was stable enough to obtain the HD product **15** in good yield (Scheme 8) without migration of the protecting group. But also with this substrate no HD prevention products were obtained (Scheme 8). When HD prevention at elevated temperatures (0 °C, dry THF, 3.3 equiv of LDA, 3.3 equiv of TMSCl) was studied the protecting group was lost which was not the case at low temperatures (−80 °C). However, it did not undergo migration of any kind (inter- or intramolecular) as was the case with the pivaloyl-protected substrate.

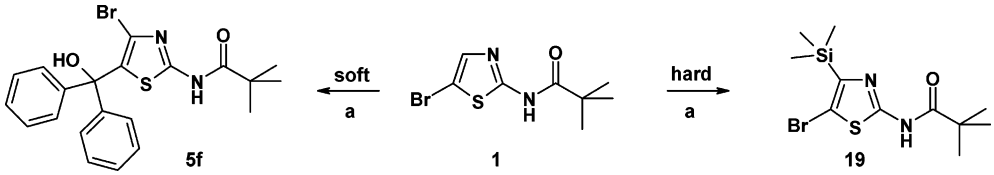
In the next series of experiments, we intended to study the effect of a second electron-withdrawing substituent

SCHEME 9. Protection of 16 and HD of 17[a]



[a] Key: (a) DMAP, BOC-anhydride, THF, reflux; (b) LDA, TMSCl, THF.

SCHEME 10. HD Prevention on 1[a]



[a] Key: (a) (1) 3.3 equiv of LDA + 3.3 equiv of electrophile, −80 °C, THF; (2) 1 equiv of **1**, −80 °C to rt.

at the amide nitrogen possibly promoting faster lithiation at 4-position of the thiazole system. As a test compound we chose the bis-BOC compound **17** since it was readily available from 5-bromo-2-thiazolamine (**16**) (Scheme 9). To further promote HD prevention the amount of LDA was increased to 6 equiv and THF and THP were studied as solvents. The reactions were carried out in a range between −60 and 0 °C in both solvents. However, prevention of the HD was not possible as again complete halogen migration occurred within minutes. One of the BOC groups was lost during workup.

In Situ Trapping of Initially 4-Lithiated Thiazoles. From the above findings, the HD reaction seems to be very fast, even at low temperatures. Therefore, the whole process is already finished before the electrophile is added to the reaction mixture. The only remaining option to prevent HD—if possible at all—was to carry out the lithiation step in the presence of a compatible electrophile.[20] For this final experiment, we chose once again TMSCl as reactant, based on its stability toward LDA and its usually fast reaction. A solution of LDA was prepared and TMSCl was added at −80 °C, followed by the 5-bromo compound **1**. Under these conditions we finally succeeded to obtain the corresponding prevention product **19** in 67% yield (Scheme 10). Compound **19** was formed exclusively, and no HD product was found in the reaction mixture. On the other hand, when a soft electrophile was used, namely benzophenone, under the same conditions no prevention product was observed and only the HD product **5f** was isolated. We therefore believe that not only the applied reaction conditions but also the properties of the electrophile have a significant influence on the type of product formed. It seems to be the case that a soft electrophile like benzophenone reacts too slow and HD takes place before the benzophenone is attacked by the initially lithiated species.

Conclusion

During our investigations, we optimized the reaction conditions for complete HD on the investigated systems. We also demonstrated that various electrophiles can be introduced in the 5-position creating in the same step a new reactive center in the 4-position. On the other hand, we showed that prevention of the HD is very difficult and only possible under certain conditions with electrophiles stable and reactive enough under such conditions. We found that TMSCl as a hard electrophile was suitable for this purpose but when benzophenone as a soft electrophile was applied under the same reaction conditions only HD product was isolated.

Experimental Section

General Bromination Procedure. The corresponding N-protected 2-thiazolamine substrate was stirred with NEt_3 (1.5 equiv) in dry $CHCl_3$, and Br_2 (1.5 equiv) was added dropwise at room temperature as a 1:1 mixture in the solvent. The reaction mixture was stirred at room temperature for 3 h and subsequently washed with satd Na_2CO_3 solution, satd $Na_2S_2O_5$ solution, water, and brine. The aqueous solutions were all re-extracted with $CHCl_3$. The combined organic layers were dried over Na_2SO_4 and filtered, and the solvent was evaporated. Recrystallization from DIPE (diisopropyl ether) or purification by MPLC (medium-pressure liquid chromatography) using silica gel as stationary phase and EtOAc and PE (petroleum ether) as mobile phase gave the desired products.

***N*-(5-Bromothiazol-2-yl)-2,2-dimethylpropanamide, 1:** mp 127−129 °C; 84% (6.0 g, 22.80 mmol, beige solid); recrystallized from DIPE; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.32 (s, 9H), 7.36 (s, 1H), 9.66 (bs, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 27.0 (q), 39.0 (s), 103.6 (s), 137.6 (d), 159.6 (s), 176.7 (s). Anal. Calcd for $C_8H_{11}BrN_2OS$: C, 36.51; H, 4.21; N 10.65. Found: C, 36.76; H, 4.16; N, 10.56.

***N*-(5-Bromothiazol-2-yl)-2,2-dimethyl-*N*-phenylpropanamide, 9:** mp 142−144 °C; 79% (0.37 g, 1.09 mmol, beige solid); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.10 (s, 9H), 7.29−7.39 (m, 3H), 7.48−7.57 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 29.0 (q), 41.7 (s), 104.8 (s), 129.2 (d), 129.7 (d), 130.9 (d), 138.1 (d), 162.2 (s), 177.1 (s). Anal. Calcd for $C_{14}H_{15}BrN_2OS$: C, 49.57; H, 4.46; N, 8.26. Found: C, 49.79; H, 4.40; N, 8.23.

***N*-(5-Bromothiazol-2-yl)-*N*-phenylcarbamic acid 1,1-dimethylethyl ester, 14:** mp 117−119 °C; 47% (606 mg, 1.71 mmol, yellow solid); MPLC PE/EtOAc 8:1; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.43 (s, 9H), 7.18−7.27 (m, 3H), 7.38−7.52 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 28.0 (q), 83.9 (s), 103.3 (s), 128.4 (d), 128.5 (d), 129.3 (d), 138.3 (s), 138.8 (d), 152.7 (s), 162.1 (s).

General Procedure for the Halogen Dance Reaction. One equivalent of the halide was added dropwise to 3.3 equiv of LDA in dry THF at 0 °C, and the reaction mixture was stirred for 15 min until TLC control showed complete HD reaction. Then 3.3 equiv of the corresponding electrophile was added at rt and the reaction mixture stirred overnight. The reaction mixture was diluted with EtOAc, washed with 2 N

HCl, water, and brine, dried over Na_2SO_4, and filtered and the solvent evaporated. Purification by MPLC or recrystallization from DIPE gave the corresponding products.

***N*-(4,5-Dibromothiazol-2-yl)-2,2-dimethylpropanamide, 2:** mp 112−114 °C; 93% (6.05 g, 17.69 mmol, brown solid); MPLC DIPE; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.31 (s, 9H), 9.03 (bs, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 27.0 (q), 39.1 (s), 101.8 (s), 123.7 (s), 158.3 (s), 176.7 (s). Anal. Calcd for $C_8H_{10}Br_2N_2OS\cdot0.15C_6H_{14}O$ (DIPE): C, 29.91; H, 3.41; N, 7.84. Found: C, 29.96; H, 3.26; N, 7.88.

***N*-(4-Bromothiazol-2-yl)-2,2-dimethylpropanamide, 3:** pale yellow, slowly crystallizing (from DIPE) solid; mp 90−97 °C; 99% (0.50 g, 1.90 mmol); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.32 (s, 9H), 6.85 (s, 1H), 8.93 (bs, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 27.1 (q), 39.1 (s), 111.3 (d), 120.8 (s), 158.7 (s), 176.4 (s). Anal. Calcd for $C_8H_{11}BrN_2OS$: C, 36.51; H, 4.21; N, 10.65. Found: C, 36.74; H, 4.06; N, 10.54.

***N*-(4-Bromo-5-formylthiazol-2-yl)-2,2-dimethylpropanamide, 5a:** mp 219−221 °C; 92% (1.02 g, 3.50 mmol, colorless solid); MPLC PE/EtOAc 4:1; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.34 (s, 9H), 9.13 (bs, 1H), 9.94 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 27.0 (q), 39.5 (s), 126.6 (s), 133.0 (s), 163.7 (s), 176.8 (s), 183.3 (d). Anal. Calcd for $C_9H_{11}BrN_2O_2S$: C, 37.13; H, 3.81; N, 9.62. Found: C, 36.97; H, 3.83; N, 9.34.

***N*-[4-Bromo-5-(1-hydroxycyclohex-1-yl)thiazol-2-yl]-2,2-dimethylpropanamide, 5b:** mp 147−149 °C; 73% (0.50 g, 1.39 mmol, colorless powder); MPLC PE/EtOAc 10:1; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.30 (s, 9H), 1.60−2.25 (m, 10H), 2.65 (bs, 1H), 8.88 (bs, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.7 (t), 25.0 (t), 27.1 (q), 36.9 (t), 39.1 (s), 72.1 (s), 114.4 (s), 135.9 (s), 156.1 (s), 176.1 (s). Anal. Calcd for $C_{14}H_{21}BrN_2O_2S$: C, 46.54; H, 5.86; N, 7.75. Found: C, 46.66; H, 5.60; N, 7.56.

***N*-(4-Bromo-5-iodothiazol-2-yl)-2,2-dimethylpropanamide, 5c:** mp 127−129 °C; 76% (5.61 g, 14.44 mmol, pale yellow solid); MPLC PE/EtOAc 10:1; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.31 (s, 9H), 8.97 (bs, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 27.0 (q), 39.0 (s), 66.9 (s), 130.1 (s), 162.5 (s), 176.6 (s). Anal. Calcd for $C_8H_{10}BrIN_2OS$: C, 24.70; H, 2.59; N, 7.20. Found: C, 25.00; H, 2.67; N, 7.22.

***N*-[4-Bromo-5-(hydroxyphenylmethyl)thiazol-2-yl]-2,2-dimethylpropanamide, 5d:** mp 154−156 °C; 86% (0.60 g, 1.63 mmol, beige solid); MPLC PE/EtOAc 10:1; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.28 (s, 9H), 2.48 (bs, 1H), 6.09 (s, 1H), 7.28−7.42 (m, 3H), 7.45−7.53 (m, 2H), 8.81 (bs, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 27.0 (q), 39.1 (s), 70.5 (d), 118.8 (s), 125.9 (d), 128.2 (d), 128.7 (d), 131.2 (s), 141.7 (s), 158.3 (s), 176.4 (s). Anal. Calcd for $C_{15}H_{17}BrN_2O_2S$: C, 48.79; H, 4.64; N, 7.59. Found: C, 48.82; H, 4.54; N, 7.54.

***N*-(4-Bromo-5-trimethylsilylthiazol-2-yl)-2,2-dimethylpropanamide, 5e:** mp 199−201 °C; 74% (0.189 g, 0.56 mmol, colorless crystals); MPLC PE/EtOAc 10:1; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.37 (s, 9H), 1.30 (s, 9H), 9.50 (bs, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ −0.8 (q), 27.0 (q), 39.2 (s), 121.4 (s), 126.6 (s), 162.1 (s), 176.7 (s). Anal. Calcd for $C_{11}H_{19}BrN_2OSSi$: C, 39.40; H, 5.71; N, 8.35. Found: C, 39.68; H, 5.66; N, 8.13.

***N*-[4-Bromo-5-(diphenylhydroxymethyl)thiazol-2-yl]-2,2-dimethylpropanamide, 5f:** mp 144−145 °C; 46% (0.23 g, 0.52 mmol, colorless solid); MPLC PE/EtOAc 10:1; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.26 (s, 9H), 3.93 (bs, 1H), 7.27−7.43 (m, 10H), 8.85 (bs, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 27.0 (q), 39.0 (s), 78.2 (s), 119.1 (s), 127.3 (d), 128.1 (d), 128.2 (d), 134.0 (s), 144.6 (s), 156.9 (s), 176.3 (s).

***N*-(4-Bromo-5-trimethylsilylthiazol-2-yl)-2,2-dimethyl-*N*-phenylpropanamide, 10:** mp 138−139 °C; 69% (0.16 g, 0.57 mmol, colorless solid); recrystallized from DIPE; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.37 (s, 9H), 1.09 (s, 9H), 7.28−7.38 (m, 2H), 7.43−7.53 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ −0.8 (q), 29.1 (q), 41.9 (s), 122.7 (s), 127.3 (s), 129.1 (d), 129.4 (d), 130.7 (d), 139.4 (s), 165.7 (s), 176.6 (s). Anal. Calcd for $C_{17}H_{23}BrN_2OSSi$: C, 49.63; H, 5.63; N, 6.81. Found: C, 49.83; H, 5.47; N, 6.80.

***N*-(4-Bromo-5-trimethylsilylthiazol-2-yl)-*N*-phenylcarbamic acid 1,1-dimethylethyl ester, 15:** mp 114−116 °C; 97% (0.35 g, 0.82 mmol, colorless crystals); MPLC PE/EtOAc 8:1; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.38 (s, 9H), 1.42 (s, 9H), 7.16−7.25 (m, 2H), 7.31−7.49 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ −0.7 (q), 28.0 (q), 83.7 (s), 121.7 (s), 127.2 (s), 128.1 (d), 128.3 (d), 129.1 (d), 139.0 (s), 152.8 (s), 165.2 (s). Anal. Calcd for $C_{17}H_{23}BrN_2O_2SSi$: C, 47.77; H, 5.42; N, 6.55. Found: C, 48.01; H, 5.31; N, 6.46.

***N*-(4-Bromo-5-trimethylsilylthiazol-2-yl)carbamic acid 1,1-dimethylethyl ester, 18:** mp 143−145 °C; 76% (0.07 g, 0.20 mmol, pale yellow solid); MPLC PE/EtOAc 6:1; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.36 (s, 9H), 1.52 (s, 9H), 10.10 (bs, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ −0.8 (q), 28.1 (q), 82.8 (s), 119.9 (s), 126.5 (s), 152.5 (s), 164.4 (s).

***N*-[5-Bromo-3-methylthiazol-2(3*H*)-ylidene]-2,2-dimethylpropanamide, 6.** Substance **1** (0.5 g, 1.90 mmol) was dissolved in 5 mL of dry THF under argon atmosphere. A 1.2 equiv (20 mg) portion of LiH was added carefully and the reaction mixture refluxed for 30 min. Subsequently, the reaction was cooled to 0 °C, and 1.5 equiv of dimethyl sulfate (0.36 g, 2.85 mmol) was added. The reaction mixture was warmed to room temperature, diluted with EtOAc, washed with 2 N HCl, water, and brine, dried over Na_2SO_4, and filtered and the solvent evaporated. Recrystallization from DIPE gave **6**: 98% (0.52 g, 1.88 mmol, colorless crystals); mp 165−166 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.26 (s, 9H), 3.68 (s, 3H), 6.92 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 27.8 (q), 35.5 (q), 40.5 (s), 98.1 (s), 126.2 (d), 167.3 (s), 188.6 (s). Anal. Calcd for $C_9H_{13}BrN_2OS$: C, 39.00; H, 4.73; N, 10.11. Found: C, 39.14; H, 4.55; N, 10.09.

2,2-Dimethyl-*N*-phenyl-*N*-(thiazol-2-yl)propanamide, 8. Compound **7** (2.84 g, 16.1 mmol) was stirred in 50 mL of dry THF, and NaH (0.46 g, 19.3 mmol) was added in small portions over a period of 15 min. The reaction mixture was stirred at rt for 1 h, and then pivaloyl chloride (2.33 g, 19.3 mmol) was added dropwise. After being refluxed overnight, the reaction mixture was diluted with EtOAc (150 mL) and poured onto water. The organic layer was washed with 2 N HCl, water, and brine, dried over Na_2SO_4, filtered, and concentrated. MPLC PE:EtOAc 6:1 gave 3.30 g (12.67 mmol, 79%) of **8** as a pale yellow solid: mp 116−117 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.11 (s, 9H), 6.98 (d, 3.6 Hz, 1H), 7.31−7.43 (m, 3H), 7.44−7.57 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 29.0 (q), 41.7 (s), 114.6 (d), 129.0 (d), 129.2 (d), 130.7 (d), 137.4 (d), 140.0 (s), 162.7 (s), 176.8 (s). Anal. Calcd for $C_{14}H_{16}N_2OS$: C, 64.59; H, 6.19; N, 10.76. Found: C, 64.68; H, 5.93; N, 10.83.

2,2-Dimethyl-(2-phenylaminothiazol-5-yl)propan-1-one, 11. A solution of **8** in 1 mL of dry THF (0.2 g, 0.77 mmol, 1 equiv) was added dropwise at −80 °C to a solution of 1.1 equiv of LDA in 3 mL of dry THF. The reaction mixture was slowly warmed to room temperature and then poured onto water and extracted three times with EtOAc. The organic layers were combined and washed with brine, dried over Na_2SO_4, and filtered, and the solvent was evaporated. Recrystallization from DIPE gave 95% **11** (0.19 g, 0.73 mmol) as beige solid: mp 148−150 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.36 (s, 9H), 7.11−7.23 (m, 1H), 7.30−7.50 (m, 4H), 7.99 (s, 1H), 9.46 (bs, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 28.2 (q), 43.7 (s), 119.3 (d), 124.5 (d), 127.4 (s), 129.7 (d), 139.3 (s), 144.6 (d), 170.1 (s), 198.1 (s).

BOC Protection of 2-Thiazolamines 7 and 16. The corresponding 2-thiazolamine (**7** or **16**, 1 equiv) was refluxed in dry THF in the presence of a catalytic amount of DMAP. Then pyrocarbonic acid di-*tert*-butyl ester (1.5 equiv for preparation of **12**, 2.4 equiv for preparation of **17**) was dissolved in dry THF, added dropwise to the reaction mixture, and refluxed overnight. The reaction solution was poured onto ice−water and neutralized with a few drops of 2 N HCl. The resulting solution was extracted three times with Et_2O, and the combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. If neces-

sary the product was purified by flash column chromatography using NEt_3 basic silica gel.

***N*-Phenyl-*N*-(thiazol-2-yl)carbamic acid 1,1-dimethylethyl ester, 12:** mp 103−104 °C; 82% (205 mg, 0.74 mmol, beige solid); MPLC PE/EtOAc 8:1; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.43 (s, 9H), 6.95 (d, 3.6 Hz, 1H), 7.20−7.29 (m, 2H), 7.34 (d, 3.6 Hz, 1H), 7.37−7.52 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 27.9 (q), 83.2 (s), 113.8 (d), 128.1 (d), 128.3 (d), 129.1 (d), 138.0 (d), 139.5 (s), 152.7 (s), 162.4 (s). Anal. Calcd for $C_{14}H_{16}N_2O_2S$: C, 60.85; H, 5.84; N, 10.14. Found: C, 61.12; H, 5.62; N, 10.23.

2,3-Dihydro-2-phenyliminothiazole-3-carboxylic acid 1,1-dimethylethyl ester, 13: mp 99−102 °C; 8% (as byproduct, 0.02 g, 0.07 mmol, colorless crystals); MPLC PE/EtOAc 8:1; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.60 (s, 9H), 5.89 (d, 5.4 Hz, 1H), 6.95−7.15 (m, 4H), 7.25−7.40 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 27.9 (q), 84.4 (s), 101.1 (d), 120.6 (d), 123.5 (d), 123.9 (d), 129.3 (d), 147.7 (s), 151.7 (s), 154.7 (s).

***N*-(5-Bromothiazol-2-yl)azabis(biscarbonic acid bis-1,1-dimethylethyl ester), 17:** mp 80−81 °C; 55% (1.16 g, 3.06 mmol, colorless solid); MPLC PE/EtOAc 10:1; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.51 (s, 18H), 7.37 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 27.7 (q), 85.1 (s), 105.5 (s), 139.5 (d), 149.3 (s), 158.5 (s).

***N*-(5-Bromo-4-trimethylsilylthiazol-2-yl)-2,2-dimethylpropanamide, 19.** To a solution of 3.3 equiv of LDA was added 3.3 equiv of TMSCl at −80 °C. Compound **1** (0.2 g, 0.76 mmol, 1 equiv) was added at the same temperature and the reaction mixture stirred at −80 °C for 30 min. After the mixture was warmed to rt within 1 h water was added and the resulting mixture extracted three times with EtOAc. The organic layers were combined and washed with brine, dried over Na_2SO_4, and filtered, and the solvent was evaporated. Subsequent MPLC PE/EtOAc 10:1 gave **19** (0.17 g, 0.51 mmol, colorless solid): mp 170−172 °C; 67%; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.36 (s, 9H), 1.32 (s, 9H), 8.78 (bs, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ −0.9 (q), 27.1 (q), 39.0 (s), 111.3 (s), 151.5 (s), 158.4 (s), 176.1 (s). Anal. Calcd for $C_{11}H_{19}BrN_2OSSi\cdot 0.27C_6H_{14}O$ (DIPE): C, 41.77; H, 6.33; N, 7.72. Found: C, 42.03; H, 5.95; N, 8.20.

Single-Crystal X-ray Diffraction Analysis of Compounds 5d, 6, and 13. Single-crystal X-ray diffraction data for compound **5d** were collected with a Philips PW1100 four-circle diffractometer and for compounds **6** and **13** with a Bruker AXS Smart CCD diffractometer, both instruments operating with graphite-monochromatized Mo Kα radiation. Structure solution and refinement was performed with the Bruker AXS SHELXTL software. Full crystallographic data are given in the Supporting Information.

Compound 5d: $C_{15}H_{17}BrN_2O_2S$, FW = 369.28, crystals from ethanol, monoclinic, C2/*c*, a = 21.693(2) Å, b = 7.426(1) Å, c = 21.271(2) Å, β = 111.72(1)°, V = 3183.5(4) Å^3, Z = 8, T = 298 K, R1 = 0.041 for 2290 observed reflections ($I > 2\sigma(I)$) and 195 parameters. The structure contains one kind of molecules mutually linked via intermolecular hydrogen bonds O(1)−H(1o)- - -N(1′) and N(2)−H(2n)- - -O(1′).

Compound 6: $C_9H_{13}BrN_2OS$, FW = 277.18, crystals from ethanol, monoclinic, $P2_1/m$, a = 11.978(1) Å, b = 7.115(1) Å, c = 14.319(2) Å, β = 99.461(2)°, V = 1203.7(2) Å^3, Z = 4, T = 297 K, R1 = 0.041 for 1735 observed reflections and 164 parameters. The structure contains two independent molecules of symmetry C_s with similar bond lengths and conformation.

Compound 13: $C_{14}H_{16}N_2O_2S$, FW = 276.35, crystals from ethanol, monoclinic, $P2_1/c$, a = 9.010(1) Å, b = 10.954(1) Å, c = 30.086(2) Å, β = 91.797(2)°, V = 2870.4(4) Å^3, Z = 8, T = 173 K, R1 = 0.050 for 3968 observed reflections ($I > 2\sigma(I)$) and 349 parameters. The structure contains two independent molecules of similar bond lengths but notably different conformation with respect to phenyl ring orientation.

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Supporting Information Available: X-ray crystal structure data for compounds **5d**, **6**, and **13** including crystallographic tables, ORTEP diagrams, and CIF files as well as ^{1}H−^{13}C and DEPT (where of importance) NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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