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A Novel Entry toward 2-Imino-1,3-thiazolidines and 2-Imino-1,3-thiazolines by Ring Transformation of 2-(Thiocyanomethyl)aziridines

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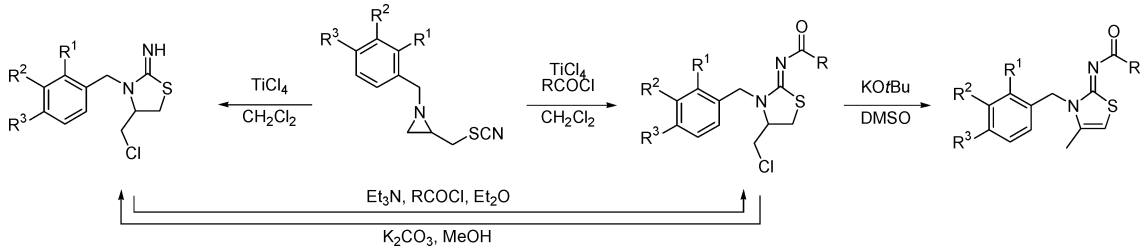

A new, efficient, and straightforward synthesis of 3-arylmethyl-4-chloromethyl-2-imino-1,3-thiazolidines and 2-(*N*-acylimino)-3-arylmethyl-4-chloromethyl-1,3-thiazolidines has been developed by ring transformation of 1-arylmethyl-2-(thiocyanomethyl)aziridines upon treatment with a catalytic amount of titanium(IV) chloride in dichloromethane. The latter 2-(thiocyanomethyl)-aziridines were prepared in high yields from 1-arylmethyl-2-(bromomethyl)aziridines by reaction with potassium thiocyanate in DMF. The 2-imino-1,3-thiazolidines and 2-(*N*-acylimino)-1,3-thiazolidines thus obtained can be easily interconverted, either by treatment with an acid chloride and a base in ether toward 2-(*N*-acylimino)thiazolidines or by treatment with potassium carbonate in methanol toward N-deprotected 2-iminothiazolidines. Dehydrohalogenation of 2-(*N*-acylimino)-3-arylmethyl-4-chloromethyl-1,3-thiazolidines by means of potassium *tert*-butoxide in DMSO afforded 2-(*N*-acylimino)-4-methyl-2,3-dihydro-1,3-thiazolines in good yields.

Introduction

The enhanced prevalence of infectious diseases and the rapid emergence of multi-drug-resistant strains has become a major concern in medicine worldwide, and this evolution has imposed a significant threat upon public health. Therefore, the development of new potential drugs to counteract the advancing resistance is one of the key issues and challenges for medicinal chemistry and related disciplines nowadays. In view of the fact that heterocyclic compounds in general and thiazolidines and thiazolines in particular exhibit a wide variety of biological activities, the search for new strategies toward the latter entities is of significant importance. An impressive list of physiological activities illustrates the relevance of 2-imino-1,3-thiazolidines and 2-imino-1,3-thiazolines as target compounds in organic synthesis. 2-Imino-1,3-thiazolidines are known and appreciated for their anti-inflammatory, anodyne, and anti-Alzheimer activity.[1] Some thiazolidines are also used in agriculture as pesticides, such as the insecticide thiacloprid,[2] and others against γ-radiation as a result of their protective properties.[3] The unsaturated 2-imino-1,3-thiazolines in their turn have also drawn the attention of the pharmaceutical chemistry, featuring important biological activities such as antimicrobial, anti-inflammatory, antihistaminic, antihypertensive, hypnotic, and anticonvulsant activity, and very recently for their applicability for the identification of human cells with positive myeloperoxidase reactivity.[4] Furthermore, thiazolines have interesting applications in agriculture as acaricides, insecticides, and plant growth regulators.[5]

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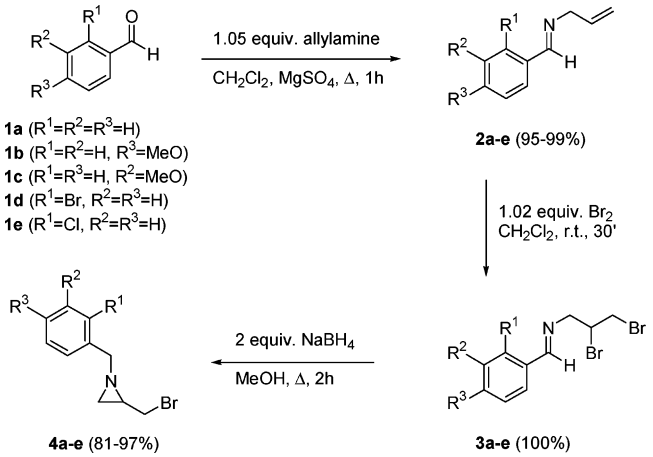
In the literature, several strategies for the synthesis of thiazolidines and thiazolines are known. A general approach toward 2-imino-1,3-thiazolidines involves the intramolecular cyclization of *N*-(2-hydroxyethyl)thiourea derivatives in acetic medium or, alternatively, in the presence of triphenylphosphine and diethyl azodicarboxylate.[6] 2-Imino-1,3-thiazolidines have also been prepared from aziridines upon treatment with thiocyanuric acid,[7] from 2-vinylaziridines in reaction with phenylisothiocyanate,[8] and from 1-(phenylthiocarbamoyl)aziridines upon treatment with sodium iodide or acid catalysis,[9] although the latter transformation gave rise to 2-amino-4,5-dihydro-1,3-thiazoles rather than the isomeric 2-iminothiazolidines. The first reports on the synthesis of 2-imino-1,3-thiazolines were published more than a century ago and comprise condensation reactions of α-haloketones with thiourea, in neutral or basic medium, or with ammonium thiocyanate.[10] The condensation reaction of α-haloketones with thiourea under acidic conditions gave rise to 2-iminothiazolines in addition to variable amounts of aminothiazoles as side-products. The problem of isomerism emerged when it was observed that methylation of the products obtained from condensation of α-haloketones with thiourea or with ammonium thiocyanate resulted in 2-imino-3-methylthiazolines.[10a,11] NMR studies a few decades ago confirmed that the initially reported condensation products were in fact 2-amino-4,5-dihydrothiazoles rather than the tautomeric 2-iminothiazolines.[12] At present, the best entries to 2-imino-1,3-thiazolines involve, first, alkylation of 2-aminothiazoles obtained from the condensation of α-haloketones with thiourea,[11] second, the condensation of α-haloketones with *N*-benzoyl *N*-substituted thioureas,[13] and third, the reaction of α-bromoketimines with potassium thiocyanate.[14] Less general approaches involve the reaction of ketones with *N*-alkyl rhodanamines or bisbenzyl formamidine disulfide[15] or the reaction of α-chloroketones with thiosemicarbazide in acid medium.[16]

SCHEME 1



In this report, a new, efficient, and straightforward synthesis of both 2-imino-1,3-thiazolidines and 2-imino-1,3-thiazolines is reported, starting from 1-arylmethyl-2-(bromomethyl)aziridines via ring transformation of 1-arylmethyl-2-(thiocyanomethyl)aziridines in high overall yields and without the formation of undesired side products.

Results and Discussion

1-Arylmethyl-2-(bromomethyl)aziridines **4** are readily available substrates, suitable for diverse applications in organic synthesis, prepared in a three-step procedure starting from the appropriate aldehydes **1** (Scheme 1).[17] Condensation of benzaldehydes **1** with 1.05 equiv of allylamine in dichloromethane in the presence of magnesium sulfate afforded the corresponding *N*-allylimines **2** in excellent yields (95−99%), which were distilled and subsequently brominated by bromine in dichloromethane to give *N*-(arylmethylidene)-2,3-dibromopropylamines **3** in a quantitative yield. The latter dibromoimines **3** were used as such because of their instability and hence treated with 2 equiv of sodium borohydride in methanol under reflux for 2 h, furnishing 1-arylmethyl-2-(bromomethyl)aziridines **4** in high yields via reduction of the

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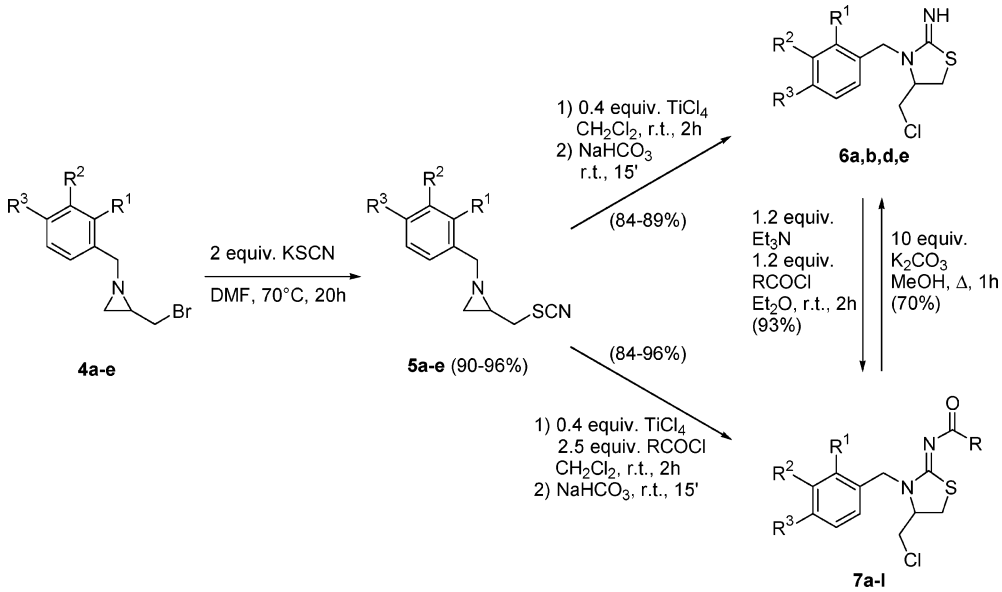
SCHEME 2



imino bond and intramolecular nucleophilic substitution (Scheme 1). The various nucleophilic interactions with the constrained heterocyclic ring and with the halogenated carbon atom of aziridines **4**, combined with the nucleophilicity of the aziridine nitrogen lone pair, allow useful (intramolecular) reactions for the construction of a variety of heterocyclic compounds. Despite the inherent synthetic potential of 1-arylmethyl-2-(bromomethyl)aziridines **4**, the reactivity of these substrates has hardly been investigated in the literature up to now.

N-Activated aziridines, such as 1-arenesulfonylaziridines, are prone to undergo ring opening reactions upon treatment with nucleophiles, resulting in a variety of acyclic amines depending on the choice of the nucleophile.[18] Analogously, 1-arenesulfonyl-2-(bromomethyl)-aziridines suffer ring opening upon treatment with a nucleophile followed by intramolecular displacement of bromine, instead of direct nucleophilic substitution.[19] 1-Alkylaziridines, however, are much less susceptible to ring opening as a result of the absence of an electron-withdrawing group at nitrogen, and treatment of 1-alkyl-2-(bromomethyl)aziridines with one or more equivalents of a nucleophile affords the corresponding 2-substituted aziridines through a direct nucleophilic substitution at the bromomethyl unit.[20]

Treatment of 1-arylmethyl-2-(bromomethyl)aziridines **4** with 2 equiv of the ambident nucleophile potassium thiocyanate furnished 1-arylmethyl-2-(thiocyanomethyl)-aziridines **5** in excellent yields (90−96%) after heating for 20 h at 70 °C in DMF (Scheme 2). When the reaction time was reduced to 10 or 15 h, small amounts of starting material were still present. These 2-(thiocyanomethyl)-aziridines **5** constitute a new and interesting class of substrates for the synthesis of heterocyclic compounds via intramolecular cyclization reactions due to the presence of an electrophilic center in δ-position of the nucleophilic nitrogen atom. Indeed, addition of a catalytic amount of the Lewis acid titanium(IV) chloride to a solution of 2-(thiocyanomethyl)aziridines **5** in dichloromethane afforded 3-arylmethyl-4-chloromethyl-2-imino-1,3-thiazolidines **6** as single reaction products in high yields (84−89%) after stirring for 2 h at room temperature. When a diluted aqueous hydrogen chloride solution (2 N) was used instead of $TiCl_4$, the isolated yield amounted only 60%. Prolonged reaction times did not result in improved yields. This reaction probably proceeds through the formation of a bicyclic aziridinium salt **8** resulting from a nucleophilic attack of the lone pair of nitrogen onto the electrophilic carbon atom of the thiocyano group, which is activated by the Lewis acid. Subsequently, this aziridinium intermediate **8** undergoes ring opening by chloride, furnishing a heterocyclic moiety (Scheme 3). Although two possible pathways might occur, only the route leading to a five-membered ring **6** appears favorable (route a), since no traces of 2-imino-1,3-thiazines **9** were detected (route b). The structural identity of the isolated compounds **6** was confirmed by detailed spectroscopic analysis and by comparison of the NMR data with literature references for analogous compounds.[14] It is noteworthy that the very sticky reaction mixture, obtained after treatment of aziridines **5** with $TiCl_4$ and stirring for 2 h at room temperature, had to

SCHEME 3

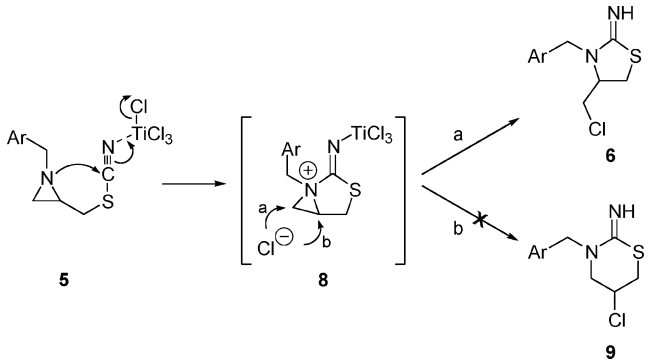


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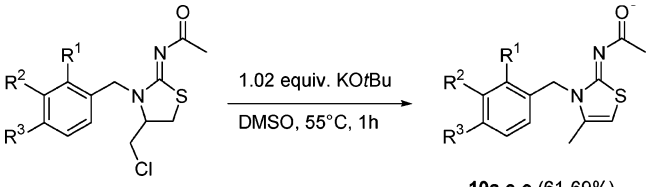
TABLE 1. Synthesis of 2-(*N*-Acylimino)-3-arylmethyl-4-chloromethyl-1,3-thiazolidines 7 from Aziridines 5

aziridines **5**	R^1	R^2	R^3	R	thiazolidines **7**	yield (%)
5a	H	H	H	Me	**7a**	95
5b	H	H	MeO	Me	**7b**	96
5c	H	MeO	H	Me	**7c**	94
5d	Br	H	H	Me	**7d**	95
5e	Cl	H	H	Me	**7e**	96
5a	H	H	H	Ph	**7f**	92
5b	H	H	MeO	Ph	**7g**	91
5e	Cl	H	H	Ph	**7h**	88
5b	H	H	MeO	EtO	**7i**	87
5c	H	MeO	H	EtO	**7j**	84
5d	Br	H	H	MeO	**7k**	91
5e	Cl	H	H	MeO	**7l**	88

be neutralized using a saturated sodium bicarbonate solution until pH 7 upon stirring for 15 min, after which the sticky paste became clear. Without this neutralization step no thiazolidines or other products could be isolated from the reaction mixtures. Attempts to purify 2-imino-1,3-thiazolidines **6** using column chromatography in order to obtain analytically pure samples failed, as these oily compounds decomposed during the attempted purification. Decomposition of thiazolidines **6** was also observed upon prolonged preservation, even at low temperatures (−20 °C).

When the same reaction was carried out in the presence of 2.5 equiv of an acid chloride, applying the original reaction conditions (i.e., 0.4 equiv of $TiCl_4$, 2 h at room temperature), the starting 2-(thiocyanomethyl)aziridines **5** were converted into 2-(*N*-acylimino)-3-arylmethyl-4-chloromethyl-1,3-thiazolidines **7** in high yields (84−96%) (Scheme 2, Table 1). Different acid chlorides were evaluated, such as acetyl chloride and benzoyl chloride, as well as methyl and ethyl chloroformate. All derivatives were isolated in high yields (Table 1). Thiazolidines **7** appeared to be highly stable upon purification by means of column chromatography and upon preservation for a long time, without any loss of purity. These features illustrate why thiazolidines **7** are very suitable target compounds in organic synthesis, especially when large amounts are needed. It should be noted that $TiCl_4$ has to be added to a solution of the starting aziridines **5** in CH_2Cl_2 before the acid chloride, and not the other way around, to obtain 2-(*N*-acylimino)-1,3-thiazolidines **7** in the highest purity. A neutralization step using a saturated sodium bicarbonate solution was necessary, otherwise no thiazolidines were isolated from the reaction mixtures. Reduction of the amount of acid chloride (1.2 instead of 2.5 equiv) resulted in the recovery of some starting material (15%). Prolonged reaction times did not result in improved yields, and heating the mixture to 40 °C resulted in complex reaction mixtures. It is noteworthy that the omission of $TiCl_4$ in these reactions gave rise to rather complex reaction mixtures in which the desired 2-imino-thiazolidines **7** were present for approximately 50%, besides a set of undesired side products. The introduction of a chloro atom into the newly formed heterocycles **7** might originate from two different sources, namely, titanium(IV) chloride on one hand and the acid chloride on the other hand. When the acid chloride was replaced by, e.g., acetic anhydride, in the presence of 0.4 equiv of $TiCl_4$, 2-acetylimino-4-chloromethyl-3-phenylmethyl-1,3-thiazolidine **7a** was isolated in 56% yield, supporting the assumption that $TiCl_4$ delivers the nucleophilic chloride.

SCHEME 4



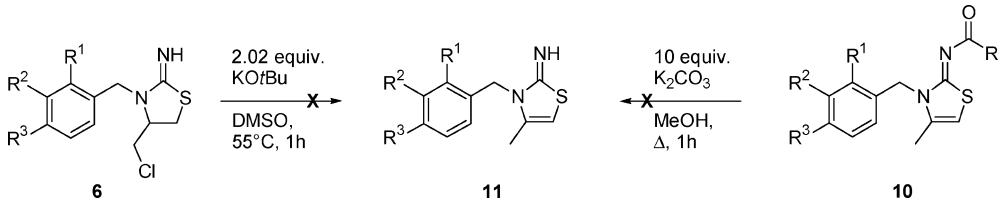
7a (R^1=R^2=R^3=H)
7c (R^1=R^3=H, R^2=MeO)
7d (R^1=Br, R^2=R^3=H)
7e (R^1=Cl, R^2=R^3=H)

10a,c-e (61-69%)

The merit of this approach concerns the possibility to interconvert 3-arylmethyl-4-chloromethyl-2-imino-1,3-thiazolidines **6** into 2-(*N*-acylimino)-3-arylmethyl-4-chloromethyl-1,3-thiazolidines **7** and vice versa. Treatment of 3-arylmethyl-4-chloromethyl-2-imino-1,3-thiazolidines **6** with 1.2 equiv of an acid chloride, e.g., acetyl chloride or benzoyl chloride, in ether in the presence of 1.2 equiv of Et_3N afforded 2-(*N*-acylimino)-3-arylmethyl-4-chloromethyl-1,3-thiazolidines **7** after stirring for 2 h at room temperature (Scheme 2). In this way, the presence of an imino group (instead of a carbonyl group) in thiazolidines **6** was demonstrated unambiguously. The opposite conversion of 2-(*N*-acylimino)-3-arylmethyl-4-chloromethyl-1,3-thiazolidines **7** into 3-arylmethyl-4-chloromethyl-2-imino-1,3-thiazolidines **6** comprises more synthetic relevance. Treatment of 2-(*N*-acylimino)-1,3-thiazolidines **7** with 10 equiv of potassium carbonate in methanol afforded 2-imino-1,3-thiazolidines **6** in 70% yield after reflux for 1 h (Scheme 2). In this way, the mostly crystalline and highly stable 2-(*N*-acylimino)-1,3-thiazolidines **7** can be prepared very easily and efficiently and converted into 2-imino-1,3-thiazolidines **6** in a simple manner whenever the latter heterocycles are desired. The presence of a chloromethyl moiety in thiazolidines **6** and **7** offers perspectives for the prospective synthesis of a large variety of 4-substituted 2-imino-1,3-thiazolidines, since the halogenated carbon atom might undergo substitution reactions by different types of nucleophiles.

An extra assignation for the molecular structure of 2-(*N*-acylimino)-1,3-thiazolidines **7** resulted from the dehydrochlorination toward 2-(*N*-acylimino)-1,3-thiazolines **10** (Scheme 4). Treatment of thiazolidines **7** with 1.02 equiv of sodium hydride in DMSO (dimsyl-Na) furnished the corresponding thiazolines **10** after heating for 1−3 h at 50−70 °C, although the reaction mixtures thus obtained contained some undesired side products in minor quantities. An excellent alternative for sodium hydride appeared to be the combination of 1.02 equiv of potassium *tert*-butoxide in DMSO, affording the pure 2-(*N*-acylimino)-4-methyl-2,3-dihydro-1,3-thiazolines **10** as single reaction products in high crude yields (95%). Purification of thiazolines **10** by means of column chromatography in order to obtain analytically pure samples proceeded in good yields (61−69%) (Scheme 4). It should be remarked that the exocyclic double bond formed upon dehydrochlorination moved from its initial position toward the endocyclic position, probably as a result of the aromatic stability of the resulting unsaturated heterocycles.

SCHEME 5



When the same dehydrochlorination procedure was applied using 2-imino-1,3-thiazolidines **6** instead of 2-(*N*-acylimino)-1,3-thiazolidines **7**, i.e. KO*t*Bu or NaH in DMSO and heating at 55 °C for 1 h, no thiazolines **11** were isolated (Scheme 5). Depending on the amount of base used, either no reaction occurred when 1 equiv of base was added or a complex reaction mixture was obtained when 2 equiv of base was added. These results confirm the unstable nature of 3-arylmethyl-4-chloromethyl-2-imino-1,3-thiazolidines **6** and might give an indication of the probably low stability of the target 2-imino-1,3-thiazolines **11**. A similar drawback was encountered when attempts were made to prepare 2-imino-1,3-thiazolines **11** starting from 2-(*N*-acylimino)-1,3-thiazolines **10** upon treatment with 10 equiv of potassium carbonate in methanol and reflux for 1 h (Scheme 5). In analogy with the conversion of 2-(*N*-acylimino)-3-arylmethyl-4-chloromethyl-1,3-thiazolidines **7** into 3-arylmethyl-4-chloromethyl-2-imino-1,3-thiazolidines **6** (Scheme 2), no thiazolines **11** were formed.

Conclusions

A novel type of ring expansion toward 3-arylmethyl-4-chloromethyl-2-imino-1,3-thiazolidines and 2-(*N*-acylimino)-3-arylmethyl-4-chloromethyl-1,3-thiazolidines has been developed by treatment of 1-arylmethyl-2-(thiocyanomethyl)aziridines with a catalytic amount of titanium(IV) chloride in dichloromethane. The latter substrates were prepared from 1-arylmethyl-2-(bromomethyl)aziridines and potassium thiocyanate in DMF in high yields, demonstrating the synthetic versatility of these constrained heterocycles. The flexibility of this approach involves the possibility to interconvert the highly stable 2-(*N*-acylimino)-3-arylmethyl-4-chloromethyl-1,3-thiazolidines into less stable 3-arylmethyl-4-chloromethyl-2-imino-1,3-thiazolidines and vice versa, either by treatment with an acid chloride and a base in ether or by treatment with potassium carbonate in methanol. Dehydrohalogenation of 2-(*N*-acylimino)-3-arylmethyl-4-chloromethyl-1,3-thiazolidines by means of potassium *tert*-butoxide in DMSO afforded 2-(*N*-acylimino)-4-methyl-2,3-dihydro-1,3-thiazolines in good yields.

Experimental Part

Synthesis of *N*-Arylmethylidene-*N*-(2-propenyl)amines 2. As a representative example, the synthesis of *N*-[(2-chlorophenyl)methylidene]-*N*-(2-propenyl)amine **2e** is described here. To a stirred solution of 2-chlorobenzaldehyde **1e** (14.05 g, 100 mmol) and anhydrous $MgSO_4$ (18.05 g, 150 mmol, 1.5 equiv) in dry dichloromethane (100 mL) was added allylamine (6.03 g, 105 mmol, 1.05 equiv) at room temperature, and the resulting mixture was stirred for 1 h under reflux. Filtration of the cooled reaction mixture and removal of the solvent in vacuo afforded *N*-[(2-chlorophenyl)methylidene]-*N*-(2-propenyl)amine **2e** (17.66 g, 99 mmol, 99%), which was purified by distillation (bp 77 °C/0.1 mmHg). The spectroscopic data of compounds **2a** and **2b** have been described elsewhere.[17c]

***N*-[(3-Methoxyphenyl)methylidene]-2-propenylamine 2c.** Colorless oil, 95% yield. Bp 75 °C/0.1 mmHg. ^{1}H NMR (270 MHz, $CDCl_3$): δ 3.84 (3H, s); 4.24−4.27 (2H, m); 5.13−5.27 (2H, m); 5.99−6.14 (1H, m); 6.95−6.99 and 7.18−7.45 (1H and 3H, 2 × m); 8.25 (1H, s). ^{13}C NMR (68 MHz, $CDCl_3$): δ 55.2, 63.4, 111.5, 116.0, 117.5, 121.5, 129.5, 135.9, 137.6, 159.8, 161.8. IR (NaCl, cm^{-1}): $\nu_{C=N}$ = 1649; ν_{max} = 3076, 2958, 2836, 1583, 1262, 919, 786, 690. MS (70 eV) *m/z* (%) 175 (M^+, 95), 174 (83), 160 (16), 144 (17), 136 (100), 107 (37), 77 (46), 68 (17), 65 (18), 51 (15), 41 (27). Anal. Calcd for $C_{11}H_{13}NO$: C 75.40; H 7.48; N 7.99. Found: C 75.22; H 7.31; N 8.13.

Synthesis of *N*-(Arylmethylidene)-2,3-dibromoopylamines 3. As a representative example, the synthesis of *N*-[(2-chlorophenyl)methylidene]-2,3-dibromopropylamine **3e** is described here. To a stirred, ice-cooled solution of *N*-[(2-chlorophenyl)methylidene]-*N*-(2-propenyl)amine **2e** (17.84 g, 100 mmol) in dry dichloromethane (150 mL) was added slowely a solution of bromine (16.31 g, 102 mmol, 1.02 equiv) in dichloromethane (50 mL) during 30 min, followed by stirring for 30 min at room temperature. Removal of the solvent in vacuo afforded *N*-[(2-chlorophenyl)methylidene]-2,3-dibromopropylamine **3e** (33.77 g, 100 mmol, 100%), which was used as such in the next step because of its lability.

***N*-[(4-Methoxyphenyl)methylidene]-2,3-dibromopropylamine 3b.** Yellow oil, 100% yield. ^{1}H NMR (270 MHz, $CDCl_3$): δ 3.83 (3H, s); 3.87 (2H, d, J = 6.3 Hz); 4.05 and 4.14 (2H, 2×d×d, J = 13.2, 5.9, 4.3 Hz); 4.48−4.57 (1H, m); 6.94 and 7.77 (2×2H, 2×d, J = 8.9 Hz); 8.26 (1H, s). ^{13}C NMR (68 MHz, $CDCl_3$): δ 34.2, 51.2, 55.4, 63.7, 114.2, 127.9, 130.5, 163.6, 164.6. IR (NaCl, cm^{-1}): $\nu_{C=N}$ = 1605; ν_{max} = 3006, 2960, 2936, 2839, 1512, 1255, 909, 832, 733. MS (70 eV): *m/z* (%) 333/5/7 (M^+, 10), 254/6 (34), 194 (17), 148 (100), 121 (72), 91 (36), 77 (13). Decomposes partially or completely upon purification.

Synthesis of 1-Arylmethyl-2-(bromomethyl)aziridines 4. As a representative example, the synthesis of 1-(2-chlorophenyl)methyl-2-(bromomethyl)aziridine **4e** is described here. To a stirred, ice-cooled solution of *N*-[(2-chlorophenyl)-methylidene]-2,3-dibromopropylamine **3e** (33.77 g, 100 mmol) in methanol (300 mL) was added sodium borohydride (7.60 g, 200 mmol, 2 equiv) in small portions, followed by a reflux period of 1 h. The reaction mixture was poured into water (100 mL), extracted with dichloromethane (3×50 mL), and dried ($MgSO_4$). Filtration of the drying agent and removal of the solvent yielded 1-(2-chlorophenyl)methyl-2-(bromomethyl)-aziridine **4e** (24.21 g, 95 mmol, 95%). The spectroscopic data of aziridines **4a** and **4b** have been described elsewhere.[17c]

2-(Bromomethyl)-1-[(3-methoxyphenyl)methyl]aziridine 4c. Light-yellow oil, 81% yield. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.64 (1H, d, J = 5.9 Hz); 1.82 (1H, d, J = 3.3 Hz); 1.91−1.98 (1H, m); 3.31 and 3.35 (2H, 2 × d × d, J = 10.2, 6.9, 6.3 Hz); 3.40 and 3.54 (2H, 2 × d, J = 13.4 Hz); 3.82 (3H, s); 6.80−6.93 and 7.22−7.28 (3H and 1H, 2 × m). ^{13}C NMR (68 MHz, $CDCl_3$): δ 35.2, 35.5, 40.2, 55.1, 64.0, 112.7, 113.5, 120.3, 129.3, 140.0, 159.6. IR (NaCl, cm^{-1}): ν_{max} = 2938, 2834, 1601, 1585, 1489, 1265, 1154, 1048, 780, 693. MS (70 eV): *m/z* (%) 255/7 (M^+, 9), 176 (26), 122 (11), 121 (100), 91 (14). Anal. Calcd for $C_{11}H_{14}BrNO$: C 51.58; H 5.51; N 5.47. Found: C 51.46; H 5.43; N 5.68.

Synthesis of 1-Arylmethyl-2-(thiocyanomethyl)aziridines 5. As a representative example, the synthesis of 1-(2-chlorophenyl)methyl-2-(thiocyanomethyl)aziridine **5e** is described here. To a solution of 2-(bromomethyl)-1-[(2-chlorophenyl)methyl]aziridine **4e** (5.21 g, 20 mmol) in dimethylformamide (55 mL) was added potassium thiocyanate (1.94 g, 40 mmol, 2 equiv) at room temperature, and the resulting mixture was stirred for 20 h at 70 °C. The cooled reaction mixture was poured in brine (100 mL) and extracted with ethyl acetate (3×50 mL). The combined organic extracts were washed with brine (50 mL) and dried with $MgSO_4$. Filtration of the drying agent and evaporation of the solvent afforded 1-(2-chlorophenyl)methyl-2-(thiocyanomethyl)aziridine **5e** (4.49 g, 18.8 mmol, 94%), wich was purified by means of column chromatography (SiO_2) (petrol ether/EtOAc/Et_3N 40/9/1, R_f 0.36).

1-Phenylmethyl-2-(thiocyanomethyl)aziridine 5a. Colorless oil, 93% yield. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.68 (1H, d, J = 6.3 Hz); 1.89 (1H, d, J = 3.3 Hz); 1.91−1.99 (1H, m); 2.85 and 3.09 (2H, 2 × d × d, J = 13.1, 7.1, 4.9 Hz); 3.46 and 3.54 (2H, 2 × d, J = 13.0 Hz); 7.25−7.38 (5H, m). ^{13}C NMR (68 MHz, $CDCl_3$): δ 34.4, 37.2, 37.3, 63.8, 111.9, 127.1, 128.0, 128.2, 138.0. IR (NaCl, cm^{-1}): ν_{SCN} = 2154; ν_{max} = 3061, 3029, 2983, 2930, 2833, 1605, 1495, 1453, 1357, 1249, 738, 699. MS (70 eV): *m/z* (%) 204 (M^+, 2), 146 (20), 91 (100), 65 (10). Anal. Calcd for $C_{11}H_{12}N_2S$: C 64.67; H 5.92; N 13.71. Found: C 64.83; H 6.14; N 13.59.

Synthesis of 3-Arylmethyl-4-chloromethyl-2-imino-1,3-thiazolidines 6. As a representative example, the synthesis of 4-chloromethyl-3-(2-chlorophenyl)methyl-2-imino-1,3-thiazolidine **6e** is described here. To a stirred, ice-cooled solution of 1-(2-chlorophenyl)methyl-2-(thiocyanomethyl)aziridine **5e** (1.19 g, 5 mmol) in dry dichloromethane (25 mL) was added dropwise titanium(IV) chloride (0.22 mL, 2 mmol, 0.4 equiv), and the resulting mixture was stirred for 2 h at room temperature. Afterward, the suspension was neutralized (pH 7) using a saturated solution of sodium bicarbonate, and the sticky paste was stirred for 15 min until the precipitate disappeared. Subsequently, the reaction mixture was filtered over Celite, the filter cake was washed with dichloromethane (3 × 20 mL), and the filtrate was extracted with dichloromethane (3 × 25 mL). The combined organic extracts were washed with brine (3 × 50 mL) and dried ($MgSO_4$). Filtration of the drying agent and removal of the solvent in vacuo afforded 4-chloromethyl-3-(2-chlorophenyl)methyl-2-imino-1,3-thiazolidine **6e** (1.18 g, 4.3 mmol, 86%, purity > 95% based on NMR).

4-Chloromethyl-3-phenylmethyl-2-imino-1,3-thiazolidine 6a. Yellow oil, 87% yield. Purity > 95% (NMR). ^{1}H NMR (270 MHz, $CDCl_3$): δ 3.22 (1H, d × d, J = 11.2, 3.0 Hz); 3.36 (1H, d × d × d, J = 11.2, 6.8, 1.0 Hz); 3.50 (1H, d × d × d, J = 11.1, 3.5, 1.0 Hz); 3.62 (1H, d × d, J = 11.1, 8.9 Hz); 3.85−3.92 (1H, m); 4.20 and 5.08 (2H, 2 × d, J = 15.5 Hz); 7.28−7.38 (5H, m); NH not detected. ^{13}C NMR (68 MHz, $CDCl_3$): δ 30.1, 41.9, 47.3, 62.0, 127.9, 128.7, 137.0, 163.0. IR (NaCl, cm^{-1}): ν_{NH} = 3327; $\nu_{C=N}$ = 1602; ν_{max} = 3092, 2952, 1494, 963, 735, 699. MS (70 eV): *m/z* (%) 241/3 (M^+ + 1, 100), 91 (5). Decomposes partially or completely upon purification.

Synthesis of 2-(*N*-Acylimino)-3-arylmethyl-4-chloromethyl-1,3-thiazolidines 7. As a representative example, the synthesis of 2-acetylimino-4-chloromethyl-3-(2-chlorophenyl)-methyl-1,3-thiazolidine **7e** is described here.

Procedure A. To a stirred, ice-cooled solution of 1-(2-chlorophenyl)methyl-2-(thiocyanomethyl)aziridine **5e** (1.19 g, 5 mmol) in dry dichloromethane (25 mL) was added dropwise titanium(IV) chloride (0.22 mL, 2 mmol, 0.4 equiv). After 5 min, acetyl chloride (0.98 g, 12.5 mmol, 2.5 equiv) was added dropwise at 0 °C, after which the mixture was stirred for 2 h at room temperature. Afterward, the suspension was neutralized (pH 7) using a saturated solution of sodium bicarbonate, and the sticky paste was stirred for 15 min until the precipitate disappeared. Subsequently, the reaction mixture was filtered over Celite, the filter cake was washed with dichloromethane (3 × 20 mL), and the filtrate was extracted with dichloromethane (3 × 25 mL). The combined organic extracts were washed with brine (3 × 50 mL) and dried ($MgSO_4$). Filtration of the drying agent and removal of the solvent in vacuo afforded 2-acetylimino-4-chloromethyl-3-(2-chlorophenyl)methyl-1,3-thiazolidine **7e** (1.52 g, 4.8 mmol, 96%), which was purified by means of column chromatography (SiO_2) (petrol ether/EtOAc 4/1, R_f 0.10).

Procedure B. To a stirred solution of 4-chloromethyl-3-(2-chlorophenyl)methyl-2-imino-1,3-thiazolidine **6e** (1.38 g, 5.0 mmol) and triethylamine (0.52 g, 5.1 mmol, 1.02 equiv) in dry dichloromethane (50 mL) was added acetyl chloride (0.40 g, 5.1 mmol, 1.02 equiv) at room temperature, followed by a stirring period of 2 h at room temperature. Afterward, the suspension was neutralized (pH 7) using a saturated solution of sodium bicarbonate, and the organic phase was washed with brine (3 × 40 mL). Drying ($MgSO_4$), filtration of the drying agent, and removal of the solvent in vacuo afforded 2-acetylimino-4-chloromethyl-3-(2-chlorophenyl)methyl-1,3-thiazolidine **7e** (1.48 g, 4.65 mmol, 93%), which was purified by means of column chromatography (SiO_2) (petrol ether/EtOAc 4/1, R_f 0.10).

2-Acetylimino-4-chloromethyl-3-phenylmethyl-1,3-thiazolidine 7a. Yellow oil, 95% yield. ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.24 (3H, s); 3.20−3.22 (2H, m); 3.49 and 3.61 (2H, 2 × d × d, J = 11.6, 8.3, 3.3 Hz); 3.92−3.95 (1H, m); 4.33 and 5.46 (2H, 2 × d, J = 15.2 Hz); 7.25−7.40 (5H, m). ^{13}C NMR (68 MHz, $CDCl_3$): δ 27.4, 30.2, 41.6, 49.2, 59.8, 127.9, 129.0, 128.1, 135.9, 170.6, 182.7. IR (NaCl, cm^{-1}): $\nu_{C=N}$ and $\nu_{C=O}$ = 1635; ν_{max} = 3064, 3030, 2940, 1513, 1401, 1249, 910, 733, 701. MS (70 eV): *m/z* (%) 282/4 (M^+ + 1, 31), 239/41 (8), 206 (33), 191 (5), 164 (8), 136 (5), 104 (19), 103 (38), 91 (100), 65 (12), 61 (13). Anal. Calcd for $C_{13}H_{15}ClN_2OS$: C 55.21; H 5.35; N 9.91. Found: C 55.06; H 5.53; N 9.84.

Synthesis of 2-(*N*-Acetylimino)-4-methyl-2,3-dihydro-1,3-thiazoles 10. As a representative example, the synthesis of 2-acetylimino-3-(2-chlorophenyl)methyl-4-methyl-2,3-dihydro-1,3-thiazole **10e** is described here. A mixture of 2-acetylimino-4-chloromethyl-3-(2-chlorophenyl)methyl-1,3-thiazolidine **7e** (0.32 g, 1 mmol) and potassium *tert*-butoxide (0.11 g, 1.02 mmol, 1.02 equiv) in DMSO (15 mL) was heated for 1 h at 55 °C. The cooled reaction mixture was poured into brine (20 mL) and extracted with diethyl ether (3 × 30 mL). The combined organic extracts were washed with brine (3 × 50 mL) and dried ($MgSO_4$). Filtration of the drying agent and removal of the solvent in vacuo afforded 2-acetylimino-3-(2-chlorophenyl)methyl-4-methyl-2,3-dihydro-1,3-thiazole **10e** (0.19 g, 0.67 mmol, 67%), which was purified by means of column chromatography (SiO_2) (petrol ether/EtOAc 7/3, R_f 0.17).

2-Acetylimino-3-phenylmethyl-4-methyl-2,3-dihydro-1,3-thiazole 10a. Colorless crystals, 69% yield. Mp 119.5 °C. R_f 0.15 (petrol ether/EtOAc 7/3). ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.17 (3H, d, J = 1.1 Hz); 2.26 (3H, s); 5.44 (2H, s); 6.23 (1H, d, J = 1.1 Hz); 6.71−6.73, 6.80−6.83 and 7.21−7.27 (2H, 1H and 1H, 3×m). ^{13}C NMR (68 MHz, $CDCl_3$): δ 14.2, 27.0, 49.0, 104.2, 126.7, 127.8, 128.8, 134.0, 135.9, 168.9, 180.5. IR (KBr, cm^{-1}): $\nu_{C=N}$ and $\nu_{C=O}$ = 1586; ν_{max} = 2924, 2854, 1476, 1367, 1281, 950, 840, 729, 694. MS (70 eV): *m/z* (%) 247 (M^+ + 1, 100), 205 (14), 91 (13). Anal. Calcd for $C_{13}H_{14}N_2OS$: C 63.39; H 5.73; N 11.37. Found: C 63.54; H 5.91; N 11.49.

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Supporting Information Available: General information and all spectroscopic data of compounds **2d,e**, **3d,e**, **4d,e**, **5b−e**, **6b−e**, **7b−l**, and **10c−e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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