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Diversity-Oriented Synthesis of a Library of Star-Shaped 2*H*-Imidazolines

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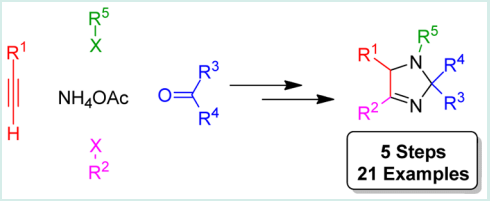
Supporting Information

ABSTRACT: A library of star-shaped 2*H*-imidazolines has been synthesized via Debus−Radziszewski condensation from 1,2-diketones and ketone starting materials. Selective reduction of one imine group of the 2*H*-imidazole intermediate with $LiAlH_4$ or catalytic flow hydrogenation furnished 2*H*-imidazolines, which could be conveniently diversified by reacting the amine *N* with electrophiles, resulting in a set of 21 amide-, carbamate-, urea-, and allylamine-containing products. In total, five points of diversification could be used, which allow the production of a set of functionally diverse compounds. The synthesis of acylated 2*H*-imidazolidines resulted in intrinsically labile compounds, which spontaneously degraded to acyclic derivatives, as shown for the reaction of 2*H*-imidazolidine with hexylisocyanate.



KEYWORDS: *aminal, Birch reduction, 1,2-diketones, diversity elements, heterocycles, imidazolines, imine reduction, protein−protein interaction*

INTRODUCTION

Over the last two decades, it has been recognized that many cellular processes are controlled by protein−protein (PPI) and peptide−protein interactions. The inhibition of such interactions has been identified as a new opportunity and paradigm in drug discovery.[1] However, high-throughput screening campaigns against PPIs with conventional libraries typically result in low hit rates, which have two obvious reasons: (1) the inhibition of PPIs is intrinsically more difficult than inhibition of an enzyme or a small-molecule binding G-protein-coupled receptor (GPCR) because PPI sites are distinguished by the cooperativity of several intermolecular interactions ("hot spots")[2] over a large surface area,[3] which (2) are poorly addressed by historical compound collections that have been optimized to hit enzymes and GPCRs with their defined and cave-like binding sites. It is generally believed that the emerging drug targets[4] of PPIs and peptide−protein interactions very likely need new types of molecules mimicking peptide segments with a larger area and multiple interaction points.[5] Among such new scaffolds, α-helix mimetics,[6] β-turn mimetics,[7] and macrocyclic structures[8] have been identified as promising synthetic goals. More recently, star-shaped molecular structures, especially 1*H*-imidazolines, have emerged as a new privileged scaffold for addressing protein−protein interactions, such as the p53-MDM2 inhibitor Nutlin-3 (**A**),[9] NF-kB inhibitor (**B**),[10] and the neuropeptide Y Y5 receptor antagonist (**C**) (Figure 1).[11] An efficient multicomponent reaction has been reported as an efficient access for this compound class, which allows the introduction of up to five substituents.[12]

Inspired by these intriguing examples, we envisioned establishing 2*H*-imidazolines as a new scaffold for library generation, which in our reasoning should have the following attractive features: (1) With its pronounced sp^3 character, it should overcome the "flatland" limitation of many heterocycles and exhibit an attractive 3D shape.[13] (2) Due to the conformational plasticity of five-membered rings, several conformations might be adaptable, which might be useful in addressing surface structures. (3) All carbon atoms are amenable for substitution and together with the amine *N* present up to five attachment points for diversity elements. (4) The two ring nitrogens should improve aqueous solubility and allow potential hydrogen bonding and polar interactions. Surprisingly, the literature contains only a few reports describing the synthesis of 2*H*-imidazolines starting from α-halogenoketones[14] or α-aminoketones,[15] by photochemical degradation of 4,5-diphenyl-2,2,6,6-tetramethyl-l,3-diazabicyclo[3.1.0]hex-3-ene,[16] by reduction of quaternary salts of 2*H*-imidazoles,[17] by cycloaddition of 2-azaallyllithium compounds with arylnitriles,[18] or by electrochemical oxidation of ketones in ammoniacal methanol.[19] To the best of our knowledge, no systematic effort has been reported to exploit this scaffold for library synthesis.

For the synthesis of our 2*H*-imidazoline library, we considered a route starting from very accessible 1,2-diketone, which in a Debus−Radziszewski reaction is transformed into 2*H*-imidazole (Figure 2). Imine reduction results in 2*H*-imidazolines, which could be diversified further by reaction of the resulting amine nucleophile with various electrophiles. This article reports our successful implementation of this flexible

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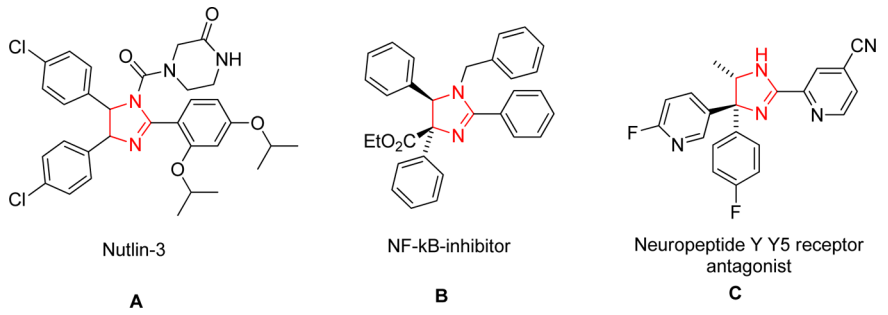


Figure 1. Structures of known 1*H*-imidazoline-based inhibitors.

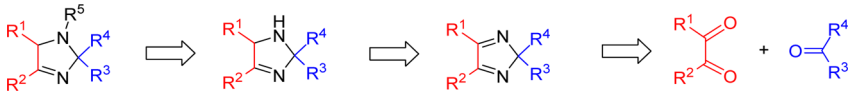
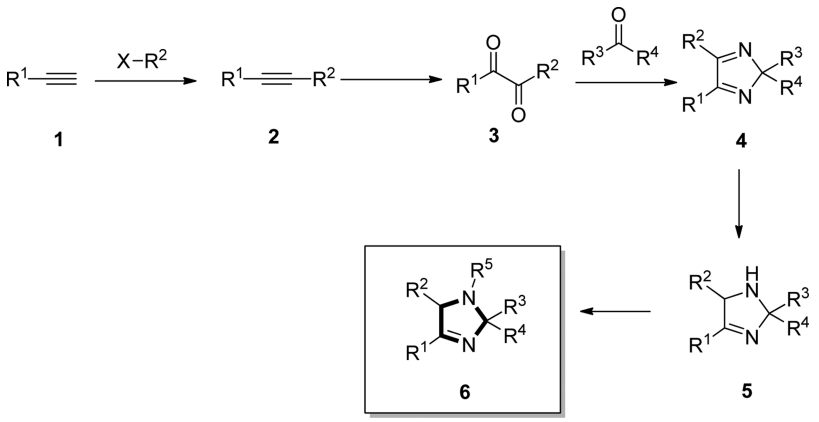


Figure 2. Access to 2*H*-imidazolines starting from 1,2-diketones.

Scheme 1. Overview of the Multistep Synthesis of a 2*H*-Imidazoline Library



synthetic strategy, offering many opportunities for diversification.

RESULTS AND DISCUSSION

Our synthetic strategy starts with 1,2-diketones for the formation of imidazoles, which we envisioned to access through oxidation of the appropriate alkyne precursors (Scheme 1). First, we used a Sonogashira coupling to functionalize the terminal alkynes **1**, furnishing disubstituted alkynes **2**. Oxidation of **2** resulted in the formation of 1,2-diketones **3**. The final step to obtain the required imidazole products **4** required a three-component reaction with a ketone and ammonia. Selective reduction of one C═N bond of **4** resulted in 2*H*-imidazolines **5**, which could then be further derivatized to target structures **6**.

For the synthesis of alkynes, a Sonogashira coupling suggested a straightforward way to connect terminal alkynes

Scheme 2. Sonogashira Coupling Reactions of Aryl Halides with Phenylacetylene 1

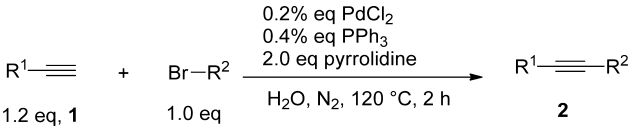


Table 1. $PdCl_2/PPh_3$-Catalyzed Sonogashira Coupling Reaction of Aryl Halides with Phenylacetylene 1

entry	R^1	R^2	product	yield (%)
1	Ph–	Ph–	**2a**	92
2	Ph–	3-Me-Ph–	**2b**	85
3	Ph–	4-MeO-Ph–	**2c**	75
4	Ph–	4-NC-Ph–	**2d**	87
5	Ph–	4-O_2N-Ph	**2e**	97
6	Ph–	2-pyridyl–	**2f**	83
7	Ph–	4-pyridyl–	**2g**	94
8	Ph–	5-pyrimidyl–	**2h**	83

Scheme 3. Oxidation of Alkynes 2 toward 1,2-Diketones 3

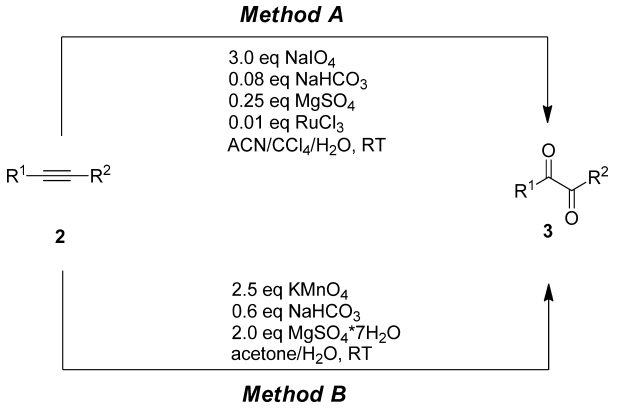


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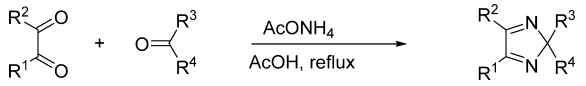
Table 2. 1,2-Diketone Products 3 Obtained via Oxidation of Disubstituted Alkynes

entry	R^1	R^2	product	method	yield (%)
1	Ph−	Ph−	**3a**	B	76
2	Ph−	3-Me-Ph−	**3b**	A	45
3	Ph−	3-Me-Ph−	**3b**	B	82
4	Ph−	4-O_2N-Ph−	**3c**	A	44
5	Ph−	4-O_2N-Ph−	**3c**	B	89
6	Ph−	4-OMe-Ph	**3d**	B	86
7	Ph−	4-pyridyl−	**3e**	B	64
8	Ph−	2-pyridyl−	**3f**	B	30

with sp^2 carbons, thereby directly leading to the appropriate starting materials for the formation of aryl-substituted 1,2-diketones. When testing several conditions for the Sonogashira reaction, we found that for our purposes the Cu-free method by Guan et al. using aqueous conditions was ideally suited[20] because it gave less homocoupling product of the terminal alkyne than all Cu-based Sonogashira conditions we tried. We synthesized eight alkynes **2a−2h** in yields between 75 and 97% with this convenient method (Scheme 2 and Table 1).

The 1,2-disubstituted alkynes obtained in the previous step served as excellent starting materials for the oxidative conversion into 1,2-diketones. For phenyl-substituted substrates, an established Ru-catalyzed method[21] using 1.0 equiv of aryl alkyne, 3.0 equiv of $NaIO_4$, 0.25 equiv of $MgSO_4$, 0.08 equiv of $NaHCO_3$, and 0.01 equiv of $RuCl_3$ in the presence of acetonitrile, CCl_4, and water resulted in complete conversion after 17−20 h at rt (Scheme 3 and Table 2, Method A). While this method proved satisfactory for the oxidation of phenyl-substituted alkynes, it completely failed for heteroaryl-substituted alkynes such as **2f**, for which no conversion could be observed even after 3 days. Fortunately, an alternative method described by Lee[22] using $KMnO_4$ as a stoichiometric oxidant in the presence of acetone proved to be a more universal approach for the oxidation of disubstituted alkynes to the corresponding 1,2-diketones (Scheme 3 and Table 2, Method B). Here the strict monitoring of the reaction progress turned out to be essential because longer reaction times led to the overoxidation of the 1,2-diketones into carboxylic acid cleavage products. The typical workup involves the reduction of unreacted $KMnO_4$ to Mn^{2+} ions by adding $NaNO_2$ and 2 M H_2SO_4 in small portions. After being stirred for 30 min, the products were extracted with ethyl acetate and subsequently purified. This workup was modified for products **3e,f** containing basic pyridine groups, which would be protonated upon addition of 2 M H_2SO_4 and therefore hardly extractable by EtOAc at that stage. When using normal workup conditions, we could only isolate 8% of product **3e**. In contrast, if we did not add $NaNO_2$ and 2 M H_2SO_4, the yield was 30%. Consequently, for **3e,f**, we skipped quenching the excess $KMnO_4$ and directly extracted the products from the reaction mixture. In summary, Method B using $KMnO_4$ resulted in substrate yields better than those with Ru-catalyzed oxidation Method A.

Scheme 5. Formation of 2*H*-Imidazoles 4 via the Debus−Radziszewski Three-Component Reaction



3 4

While this method turned out to be very effective for the oxidation of any type of aryl/hetaryl-substituted alkynes, it showed its limitations when alkyl-substituted alkynes were subjected to this oxidation reaction, for which we found an alternative access via Au(I)-catalyzed migration of 1,4-bispropargyl acetates developed by Nevado.[23] With this strategy, we synthesized 2,6-dimethylheptane-3,4-dione (**3g**) (Scheme 4). By *n*-BuLi-mediated deprotonation of the terminal alkyne and electrophilic quench with isobutyraldehyde, 2,6-dimethylhept-3-yne-2,5-diol (**7**) could be isolated in 91% yield (Scheme 4). Acetylation of **7** with Ac_2O produced diacetate **8**, which was isomerized using 0.02 equiv of [(IPr)Au(NTf_2)] in the presence of anhydrous DCM followed by ester cleavage with 2.0 equiv of K_2CO_3 and MeOH, producing 2,6-dimethylheptane-3,4-dione (**3g**) in 78% yield (64% overall yield). While the individual reaction steps progressed smoothly, the isolation of the quite volatile **3g** imposed an experimental challenge that required the careful removal of the solvent. Interestingly, after the removal of the solvents, the resulting oily residue separated into two phases, whereby the lower phase solidified. The oily supernatant was taken off with a pipet and identified as the desired product **3g**. The solid residue was identified as the reaction catalyst, which was washed with small amounts of *n*-pentane and could be recovered in a yield of 50% and reused as catalyst in subsequent isomerization experiments.

With a set of 1,2-diketones **3a−g** in hand, we could pursue the synthesis of 2*H*-imidazoles using a Debus−Radziszewski

Scheme 4. Au(I)-Catalyzed Rearrangement Leading to the Unsymmetrical Alkyl-Substituted 1,2-Diketone 3g

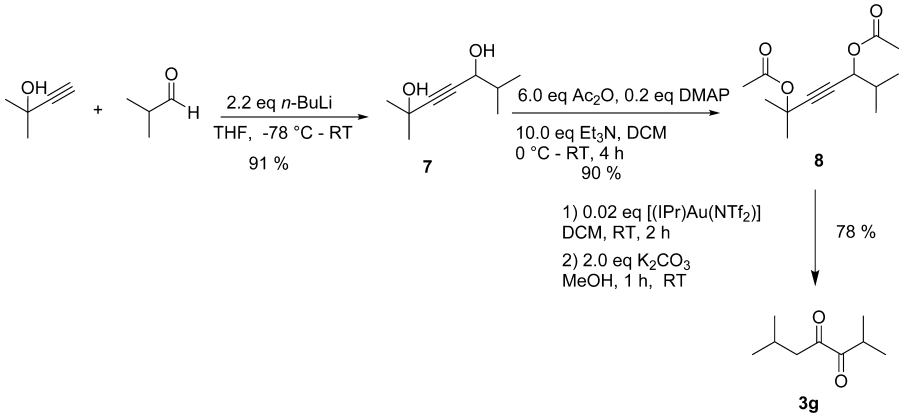


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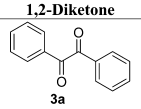
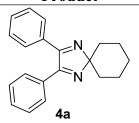
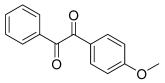
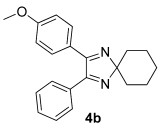
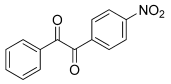
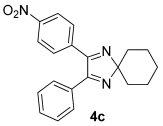
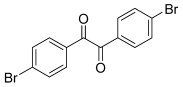
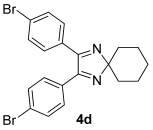
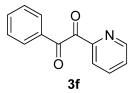
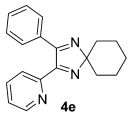
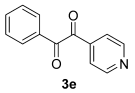
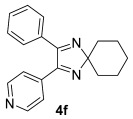
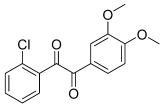
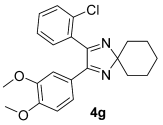
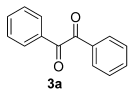
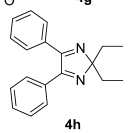
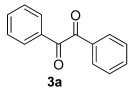
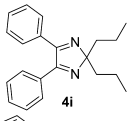
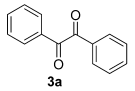
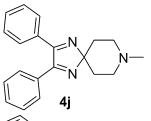
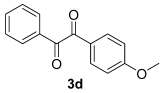
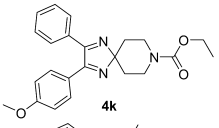
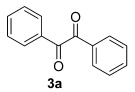
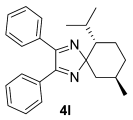
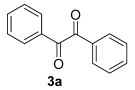
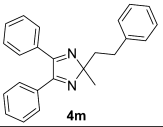
Table 3. 2*H*-Imidazoles Derived from 1,2-Diketones via the Debus−Radziszewski Three-Component Reaction

Entry	1,2-Diketone	Product	Yield (%)
1	 3a	 4a	95
2	 3d	 4b	67
3	 3c	 4c	85
4	 3f	 4d	98
5	 3f	 4e	86
6	 3e	 4f	47
7		 4g	97
8	 3a	 4h	96
9	 3a	 4i	95
10	 3a	 4j	80
11	 3d	 4k	97
12	 3a	 4l	75
13	 3a	 4m	83

three-component reaction comprising the synthesized 1,2-diketones, a ketone, and ammonium acetate (Scheme 5).[24]

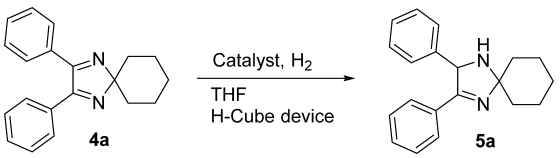
In total, we have synthesized 13 compounds based on this method in yields of 47−98%. To obtain a diverse compound library, we subjected substrates with different functional groups

Scheme 6. Reduction of 4a with Different Hydride-Reducing Reagents under Various Conditions

Table 4. Reaction Conditions for the Reduction of 2*H*-Imidazole

entry	conditions	yield of **5a** (%)
1	Et_3SiH, TFA, rt	0
2	DIBAL-H, toluene, reflux	0
3	$LiBEt_3H$, THF, 0−50 °C	0
4	$NaBH_4$, MeOH, 0−50 °C	40
5	$HSiCl_3$, DMF, DCM, 0 °C to rt	30
6	$NaBH_4$, BH_3, THF, 0 °C to rt	86
7	phthalic acid, BH_3, THF, −12 °C to rt	84
8	$LiAlH_4$, THF, 0 °C to rt, 2.5 h	81

Scheme 7. Heterogeneous Reduction of 4a to 5a Using an H-Cube Device



to the transformation. Two of the three components in the imidazole-forming reaction, the 1,2-diketones and the ketone compound, provide the opportunity to introduce a high degree of variation into the synthesis. For the 1,2-diketones, we had phenyl groups containing methoxy, nitro, bromo, and chloro substituents or featuring pyridine as hetaryl substituents to form the corresponding 2*H*-imidazole derivatives (entries 2−7, Table 3). For the second diversity-creating building block in the imidazole formation, we used different ketones, such as cyclohexanone, 3-pentanone, 4-heptanone, and 4-phenyl-2-butanone (entries 8, 9, and 13, Table 3). We also introduced basic residues derived from *N*-methyl-4-piperidone and 1-ethoxycarbonyl-4-piperidone to potentially improve the water solubility of the imidazole (entries 10 and 11, Table 3). Additionally, we decorated one of the heterocyclic product with a (−)-menthone-derived moiety to potentially discover an impact of stereochemical factors on the biological activity (entry 12, Table 3).

After the five-membered ring structure was assembled, the reduction of the C═N moiety in the 2*H*-imidazoles was the next important step to further increase the diversity of the heterocyclic library (Scheme 6). A wide range of hydride-reducing agents have been described in the literature for reducing imidazoles to their corresponding dihydro and tetrahydro counterparts. Inspired by these reports, we have applied different reducing agents under various conditions to reduce the C═N bonds, as shown in Scheme 6. As listed in Table 4, we observed that for our substrate reducing agents such as lithium triethylborohydride ($LiBEt_3H$),[25] diisobutylaluminum hydride (DIBAL-H),[26] and Et_3SiH[27] were not strong enough to mediate the desired transformation. $HSiCl_3$[28] produced **5a** in 30% yield. Interestingly, $NaBH_4$ delivered **5a**

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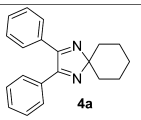
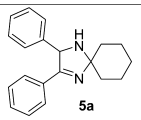
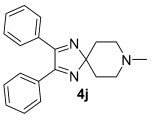
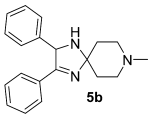
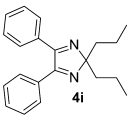
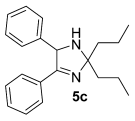
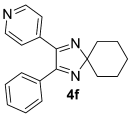
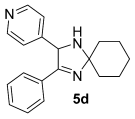
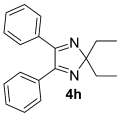
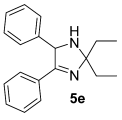
Table 5. Optimization of the Flow-Through Hydrogenation of Imidazole 4a Using the H-Cube Device

entry	catalyst	concentration (M)	flow rate (mL/min)	temperature (°C)	pressure (bar)	conversion (%)[a]
1	Raney-Ni	0.15	0.7	35	1	
2	Raney-Ni	0.15	0.7	50	10	
3	Raney-Ni	0.15	0.7	60	20	10
4	5% Pt/C	0.1	1.0	60	60	70
5	5% Pt/C	0.15	0.7	80	60	83
6	5% Pt/C	0.1	1.0	80	80	75
7	10% Pd/C	0.1	1.0	25	1	1
8	10% Pd/C	0.05	1.0	40	20	9
9	10% Pd/C	0.1	1.0	40	40	11
10	10% Pd/C	0.1	1.0	60	60	51
11	10% Pd/C	0.05	1.0	60	60	57
12	10% Pd/C	0.1	1.0	60	80	55
13	10% Pd/C	0.1	1.0	80	60	77
14	10% Pd/C	0.1	1.0	80	80	80
15	10% Pd/C	0.05	1.0	80	80	81

[a]Estimated by GC-MS analysis via integration of the TIC signals.

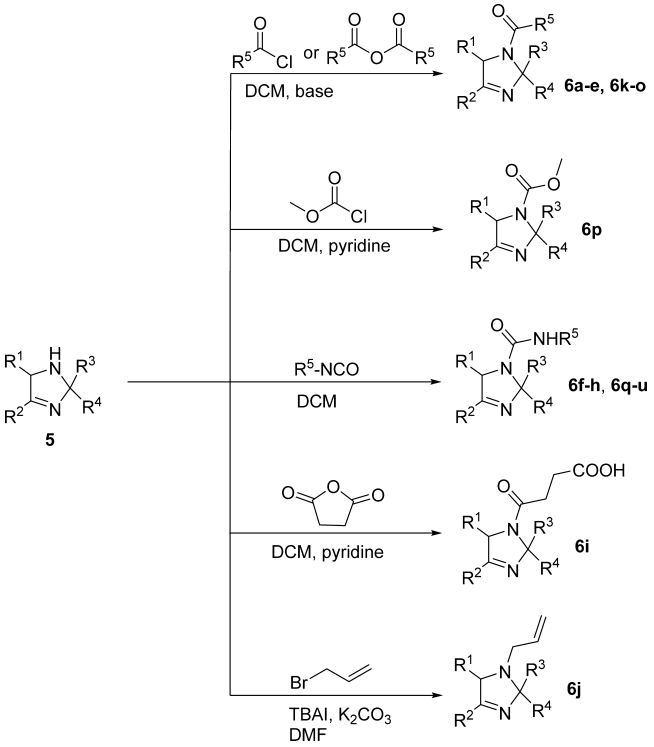
Table 6. Synthesis of Various 2*H*-Imidazolines

Entry	2*H*-Imidazole	Conditions	Product	Yield (%)
1	 4a	3.0 equiv $LiAlH_4$, THF, 0 °C-RT, 4 h	 5a	86
2	 4j	8.1 eq $LiAlH_4$, THF, 0 °C-RT, 18 h	 5b	55
3	 4i	10% Pd/C, 1.0 mL/min, 80 °C, 60 bar H_2	 5c	90
4	 4f	10% Pd/C, 2.0 mL/min, 50 °C, 40 bar H_2	 5d	24[a]
5	 4h	0.5 eq $NaBH_4$, 2 eq BH_3, THF, 0 °C-RT, 16 h	 5e	84

[a]Isolated as an 85:15 mixture of product/2*H*-imidazole.

in 40% yield, which could be further improved by adding BH_3 as a reducing agent using Opatz' conditions developed for the reduction of acyclic 1,2-diimines.[29] BH_3/phthalic acid showed equal efficiency, but ultimately, we settled on $LiAlH_4$ as a reducing agent,[30] as it gave by far the fastest reduction and decent yields. Importantly, any attempt to reduce also the second imino group by using excess reducing reagents or elevated temperatures failed, indicating that this second transformation is much more difficult to achieve, as has been observed before.[17,31] In the isolation process of **5a**, we noticed

Scheme 8. N-Acylation and N-Allylation of Imidazolines 5



that over time reoxidation to the starting material **4a** occurred. After a few days of exposure to air, the product was completely reoxidized to the starting material. This indicates that compound **5a** is not stable under these conditions and provides another explanation why full conversions in the reduction step were generally not achieved.

As an alternative to the hydride-reducing agents, we investigated the catalytic hydrogenation with heterogeneous catalysts using an H-Cube flow reactor to reduce **4a** to **5a** as a test example (Scheme 7).[32] To find the optimal reaction conditions, we used different catalysts under various conditions, as shown in Table 5. The best yield was obtained when using 5% Pt/C at 0.15 M concentration of **4a** in THF, a flow rate of 0.7 mL/min at 80 °C, and 60 bar hydrogen pressure was used (83% yield).

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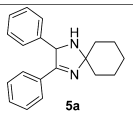
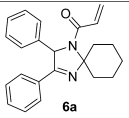
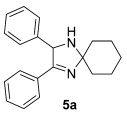
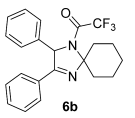
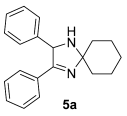
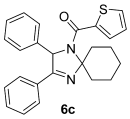
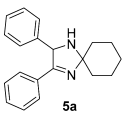
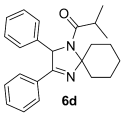
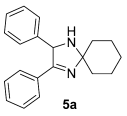
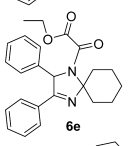
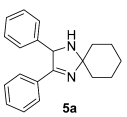
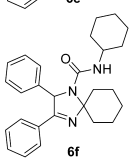
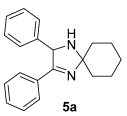
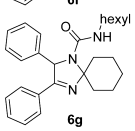
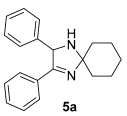
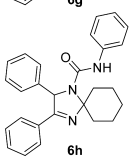
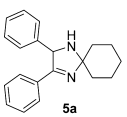
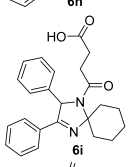
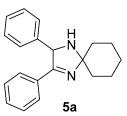
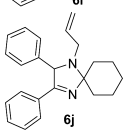
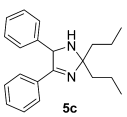
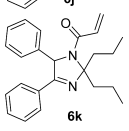
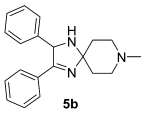
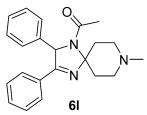
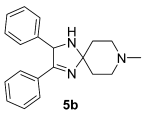
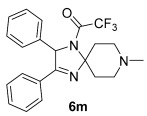
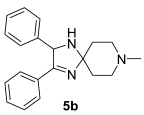
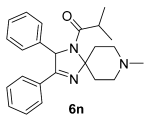
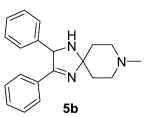
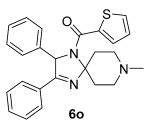
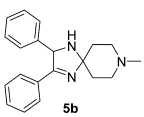
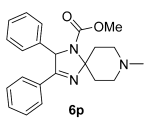
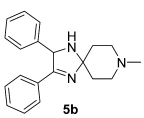
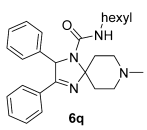
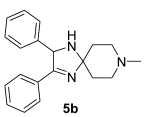
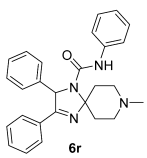
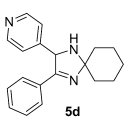
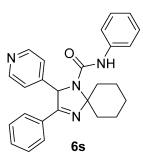
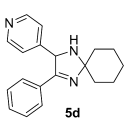
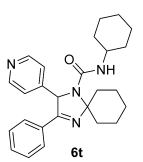
Table 7. Diversification of 2*H*-Imidazolines by Reaction with Various Electrophiles

Entry	Starting material	Conditions[a]	Products	Yield [%]
1	 **5a**	2.0 eq Et_3N, 1.2 eq acryloyl chloride, - 78 °C, 30 min	 **6a**	86
2	 **5a**	2.0 eq Et_3N, 1.2 eq TFAA anhydride, - 78 °C - RT, overnight	 **6b**	68
3	 **5a**	2.0 eq Et_3N, 1.2 eq 2-thiophenecarbonyl chloride, - 78 °C- RT, overnight	 **6c**	95
4	 **5a**	2.0 eq Et_3N, 1.9 eq isobutyryl chloride, 0 °C - RT, overnight,	 **6d**	68
5	 **5a**	10 eq pyridine, 5.1 eq ethyl 2-chloro-2-oxoacetate, 0 °C – RT, 2h	 **6e**	79
6	 **5a**	3.0 eq cyclohexylisocyanate, 0 °C - RT, overnight	 **6f**	86
7	 **5a**	3.0 eq hexylisocyanate, 0 °C - RT, 2 h	 **6g**	73
8	 **5a**	3.0 eq phenylisocyanate, 0 °C - RT, 2 h	 **6h**	78
9	 **5a**	10 eq pyridine, 6.3 eq succinic acid, 0 °C - RT, overnight	 **6i**	80
10	 **5a**	3.0 eq allyl bromide, 2.0 eq K_2CO_3, 0.1 eq TBAI, DMF 60 °C, overnight	 **6j**	86
11	 **5c**	2 eq Et_3N, 1.2 eq acryloyl chloride, - 78 °C, 30 min	 **6k**	86
12	 **5b**	23 eq pyridine, 6.6 eq acetyl chloride, - 78 °C - RT, overnight	 **6l**	82
13	 **5b**	3.4 eq Et_3N, 2.4 eq TFAA, -78 °C – RT, overnight	 **6m**	69
14	 **5b**	10 eq pyridine, 5.1 eq isobutyryl chloride, 0 °C - RT, overnight	 **6n**	65
15	 **5b**	10 eq pyridine, 5.0 eq 2-thiophenecarbonyl chloride, 0 °C - RT, overnight	 **6o**	42
16	 **5b**	19.7 eq pyridine, 4.9 eq methylchloroformiate, -78 °C - RT, overnight	 **6p**	66
17	 **5b**	3.0 eq hexylisocyanate, 0 °C - RT, overnight	 **6q**	72
18	 **5b**	3.0 eq phenylisocyanate, 0 °C - RT, overnight	 **6r**	74
19	 **5d**	3.0 eq phenylisocyanate, 0 °C - RT, overnight	 **6s**	51
20	 **5d**	3.0 eq cyclohexylisocyanate, 0 °C - RT, overnight	 **6t**	66
21	**5d**	3.0 eq hexylisocyanate, 0 °C - RT, overnight	**6u**	73

[a]All transformations were performed in dry DCM.

Using the described methods for the 2*H*-imidazole reduction, in total, five different 2*H*-imidazolines were synthesized, which are listed in Table 6. Imidazole **4i** was readily reduced to the 2*H*-imidazoline **5c** via a flow-through hydrogenation using the H-Cube device in good yield (90%). It is interesting to note that for **4f** we had to reduce the H_2 pressure from 80 to 40 bar and the temperature from 80 to 50 °C in order to not obtain the fully reduced imidazolidine (as detected via crude NMR). In contrast, compound **5d** readily reoxidized back to the corresponding 2*H*-imidazole upon workup, which explains the low yield of 24%.

2*H*-Imidazole **4a** was readily reduced to **5a** in good yield (86%), with $LiAlH_4$ as the reducing agent. Starting from **4j**, compound **5b** was achieved in an acceptable 55% yield, using the same reducing agent. For the reduction of **4h**, we used the method of Opatz with $NaBH_4/BH_3$ as the reducing agent.[29] 2*H*-Imidazoline **5e** was achieved in a good 84% yield.

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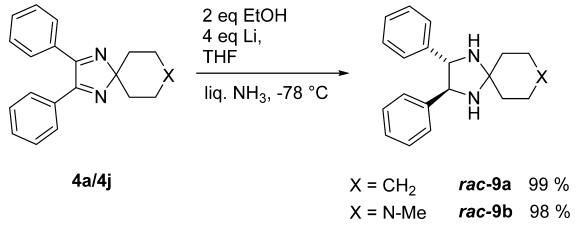
Scheme 9. Birch Reduction of Imidazole 4 to 2*H*-Imidazolidines 9



To further increase the diversity of the compound library via the introduction of additional functional groups, we used amide-, allyl-, carbamate-, and urea-forming reactions (Scheme 8 and Table 7). Our first attempts at the acylation of the free amines with acid chlorides centered on a protocol by Kanemasa (Scheme 8).[32] This method (2.0 equiv of Et_3N, 1.2 equiv of the appropriate acyl chloride, dry DCM, −78 °C) was applied for the two reactions, where acryloyl chloride was used as the electrophile. For **6a** and **6k**, yields of 86% were achieved. A slight modification (warming to rt overnight) was used for the 2-thienylacylation of **5a** to **6c** (95% yield) and for the trifluoroacetylation reactions using TFAA as the electrophile. Compound **6d** was isolated in 68% yield, and compound **6m** was isolated in 69% yield.

Acetylation of **5b** was performed under adapted conditions (2.2 equiv of pyridine, 1.6 equiv of acetyl chloride, −78 °C to rt, overnight), as ketene formation is possible for acid chlorides exhibiting an α-CH when using Et_3N as a base. A large excess of base and acetyl chloride had to be added after the reaction was stirred overnight because no conversion was detected via TLC. **6l** was isolated in a yield of 82%. The isobutyrylamide **6d** was synthesized accordingly to **6k**, but instead of −78 °C, the reaction was performed at 0 °C because isobutyryl acid chloride was expected to be a less potent electrophile. After 3.5 h, additional acid chloride had to be added and full conversion was detected overnight, resulting in 68% isolated yield for **6d**.

In an attempt to enhance reaction rates, pyridine was tested as a base; the equivalents were increased, and the reaction was run at 0 °C and warmed to rt, resulting in decent yield for **6e** (79% yield), **6n** (65%, yield), and **6o** (42% yield).

The carbamate formation of **5b** to **6p** was achieved in an acceptable yield of 66% using 19.7 equiv of pyridine and 4.9 equiv of methylchloroformiate (−78 °C to rt, overnight).

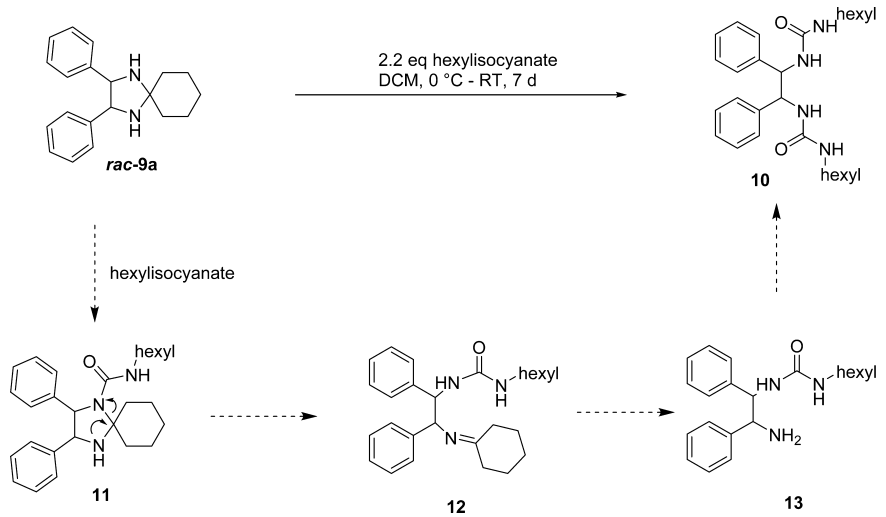
In order to gain access to the hexyl-, cyclohexyl-, and phenylurea derivatives, we used a modified protocol by Hecht.[33] Using 3.0 equiv of the appropriate isocyanate in dry DCM (0 °C to rt), six different urea derivatives (**6f−h**, **6q,r**, **6u**) were obtained with 72−86% yields. Urea substrates **6s** and **6t** were obtained in acceptable yields of 51 and 66%, respectively. These yields are being attributed to difficulties in product isolation (semipreparative HPLC had to be performed following the flash column chromatography). In order to switch the polarity of the compounds, the free carboxylic acid derivative **6i** was synthesized by adding a solution of pyridine, and 6.3 equiv of succinic anhydride was added to **5a** in dry DCM at 0 °C. Full conversion to the free carboxylic acid was detected after 16 h, furnishing **6i** in 80% isolated yield.

Having successfully synthesized various acylated imidazoline derivatives, we investigated various allylation methods to introduce the corresponding functional groups. While allyl bromide with NaH in DMF did not produce any product, switching to K_2CO_3 as base delivered the product **6j** in 57% yield. The yield of **6j** could be further improved by using 3.0 equiv of allyl bromide and 2.0 equiv of potassium carbonate in the presence of 0.1 equiv of TBAI in dry DMF at 60 °C overnight, producing 86% of **6j** (Table 7).[34]

Having established synthetic access to 2*H*-imidazolines, we explored the possibility of the second imine group being reduced, leading to 2*H*-imidazolidines featuring an aminal moiety, which we planned to stabilize via electron-withdrawing substituents. In order to obtain the desired 2*H*-imidazolidines, we had to seek alternatives to the application of metal hydrides. Inspired by the work of Corey, we used their Birch conditions (Li in liquid NH_3) for the full conversion to the 2*H*-imidazoline ***rac*-9a** (Scheme 9).[24a] The mechanism of this transformation is believed to proceed over a dianion intermediate which explains the strict selectivity for the thermodynamically more stable *trans*-product.[35] The Birch protocol delivered also piperidone derived product **9b** in equally excellent yield.

With the 2*H*-imidazolidines in hand, our initial attempts centered on additional functionalizations. To this end, we subjected ***rac*-9a** to various acyl chlorides and anhydrides under

Scheme 10. Proposed Mechanism for the Fragmentation of the Imidazolidine Ring



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standard conditions. With the exception of the successful reaction with acryloyl chloride, which had been reported before by Kanemasa,[32] we were not able to functionalize ***rac*-9a** with other acylating agents such as Ac_2O, AcCl, or TFAA and ended up with varying amounts of uncharacterized side products and starting material. When we reacted ***rac*-9a** with an isocyanate electrophile in order to produce the correspondent urea derivative, we were finally able to isolate and characterize a distinct reaction product. Treatment of 2*H*-imidazolidine ***rac*-9a** with hexylisocyanate gave acyclic diurea **10** in a yield of 64% (Scheme 10). This unforeseen reactivity might be attributed to increased conformational stress, which renders the mono- or disubstituted derivative unstable and triggers the fragmentation of the aminal moiety. Based on our observations, we speculate that the formation of **10** could occur according to the reaction pathway suggested in Scheme 10: upon treatment of ***rac*-9a** with hexylisocyanate, the urea derivative **11** is formed. The conformational strain of **11** is released upon fragmentation to **12**, additionally driven by the good leaving group tendency of the ureido moiety. While **12** could not be observed directly, we could follow the generation of intermediate **13** via HPLC-ESI-MS, which after prolonged reaction time was consumed by reaction with hexylisocyanate to furnish **10**, which could be isolated in 64% yield and fully characterized.

We believe that a similar combination of conformational stress and an improved leaving group tendency of amido and ureido groups is also responsible for the intrinsic lability of other acylated 2*H*-imidazolidine derivatives, making this compound class elusive for library synthesis and screening.

CONCLUSION

In summary, we have presented an efficient synthetic access to 2*H*-imidazolines starting from 1,2-disubstituted alkynes and a ketone as starting materials, which were converted to 2*H*-imidazoles in a three-step synthesis. Reduction of these intermediates with $LiAlH_4$ or by catalytic hydrogenation with Pd/C as catalyst led to the selective reduction of only one imino group, resulting in 2*H*-imidazolines, which could be easily diversified via acylation, alkylation, and reactions with isocyanates or chloroformiates, leading to a diverse set of compounds. Our attempts toward the fully reduced 2*H*-imidazolidines and its subsequent reaction with isocyanate led to products that showed intrinsic lability and spontaneously furnished acylic products resulting from the fragmentation of the aminal moiety. We believe that the reported star-shaped 2*H*-imidazolines represent an interesting new chemotype, which might produce interesting results when included in compound collections for biological screening.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscombsci.5b00107.

Experimental procedures and copies of ^1H NMR and ^{13}C NMR spectra of all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

DCM, dichloromethane; DMF, *N*,*N*-dimethylformamide; HPLC, high-pressure liquid chromatography; IPr, 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene; rt, room temperature; TBAI, tetrabutylammonium iodide; TFA, trifluoroacetic acid; TFAA, trifluoracetic anhydride; THF, tetrahydrofuran; TIC, total ion count; TLC, thin-layer chromatography

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