Aza-Wittig access to chiral imidazol(in)es†

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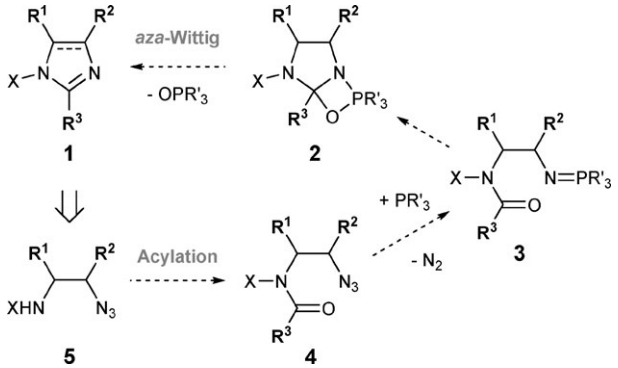
2-Imidazolines and imidazoles have been accessed by an aza-Wittig sequence featuring novel *N*-acylation methodology for sulfonamides and optimized conditions for ring closure.

Imidazole-containing alkaloids comprise a rich group of bioactive natural products[1] and constitute challenging targets for organic synthesis.[2] In contrast, the 4,5-dihydro-1*H*-imidazole (“2-imidazoline”) motif is much less common in nature,[3] but 2-imidazolines have been successfully explored in medicinal chemistry and effector molecules.[4] In addition, optically active imidazolines have been investigated as amide bond isosteres and chiral templates,[5] catalyst precursors,[6] and as ligands for asymmetric catalysis.[7]

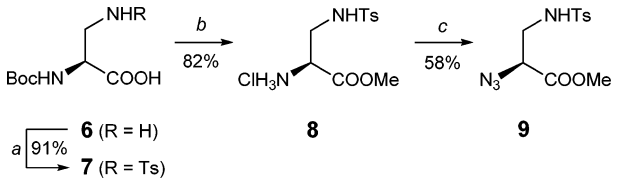
Enantiopure imidazolines can be prepared from 1,2-diamines,[6a,7a,8] amido alcohols,[9] and other starting materials,[10] by using (Lewis) acidic activation, intermediate formation of imidoyl halides or esters, or intramolecular substitution. Recently, aza-Wittig ring closures[11] have emerged as a powerful means for effecting clean heterocyclizations to oxazolines and thiazolines, even of sensitive precursors.[12] Up to now, similar transformations leading to the imidazoline homologs had to employ harsh reaction conditions or special substrates.[13] Here, we report on a general method to furnish imidazolines and imidazoles from azido peptides under very mild conditions using aza-Wittig methodology.[14]

Owing to their low electrophilicity, amide carbonyls are typically inert toward aza-Wittig reactions.[11,15] We imagined that using a chemically stable, electron-withdrawing substituent X on the nitrogen atom should render the amide carbonyl susceptible for intramolecular attack of a putative imino-phosphorane **3** (Scheme 1). By choosing a sulfonyl group for this purpose, a suitably protected product **1** would arise from **2**, which could be liberated and/or further functionalized. Iminophosphorane **3** should be accessible from azide **5** by acylation of the NHX moiety (*via* **4**) and Staudinger reaction with phosphines, thereby enabling assembly from building blocks with full regio- and stereocontrol (R^1/R^2).

To explore the feasibility of this strategy, we investigated the chiral diaminopropionic acid derivative **9** (Scheme 2) in analogy to substrates useful for the formation of peptide-embedded thiazolines and oxazolines.[12c] Conversion of commercially available (*S*)-N^{α}-Boc-diaminopropionic acid **6** into its N^{β}-sulfonamide **7** proceeded swiftly under standard conditions. Acid **7** was esterified using MeOH–$SOCl_2$ with



Scheme 1 Regioselective access to imidazol(in)es by aza-Wittig disconnection.



Scheme 2 Synthesis of azido-sulfonamide **9**. *Reagents and conditions*: (a) TsCl, 1,4-dioxane, aq. Na_2CO_3, rt; (b) MeOH, $SOCl_2$, rt; (c) TfN_3 (6 equiv.), $EtN(iPr)_2$, CH_2Cl_2–DMF, $CuSO_4$.

concomitant loss of the Boc group (**8**), and transformed into the corresponding azide **9** using modified Wong conditions (>95% ee by chiral HPLC).[16] Azide **9** was found to be rather sensitive towards exposure to base, and the reaction proceeded much better when DMF was used as cosolvent.

To the best of our knowledge, *N*-acylation of sulfonamides such as **9** is not well documented for more complex acyl donors. Primary sulfonamides have been subject to acylation with amino acids, using PyBOP[17] or amino acid fluorides.[18] *N*-Acyl sulfonamides can be formed by ligating thioacids with sulfonyl azides.[19] Precedence for secondary sulfonamide substrates is very limited;[20] hence, suitable conditions had to be found. Initially, several reagents were screened using the sterically hindered threonine derivative **10a**, with variation of base, solvent, and temperature. For example, PyBrop or carbodiimides gave low yields and/or led to extensive racemization or decomposition. However, clean acylation of **9** to **11** could be achieved by employing either acid fluorides or uronium-based coupling reagents. Selected cases are compiled in Table 1.

When freshly prepared, preformed amino acid fluoride delivered the amide **11** in acceptable yield and purity (dr > 97 : 3).[18] Both soluble organic as well as solid inorganic base could be used (see entries a and b). Unfortunately, TFFH-mediated formation[21] of the acid fluoride *in situ* gave inferior results (entry c). First experiments with the uronium salt

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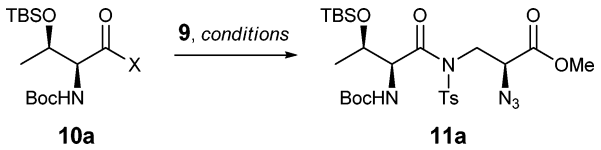
Table 1 Optimization of sulfonamide *N*-acylation



10a **11a**

Entry	X	Reagent[a]	Base	Solvent	Yield
a	F	—	$EtN(iPr)_2$	CH_2Cl_2	59%
b	F	—	Cs_2CO_3	CH_2Cl_2	51%
c	OH	TFFH	Cs_2CO_3	CH_2Cl_2	28%
d	OH	HATU	$EtN(iPr)_2$	CH_2Cl_2	14%
e	OH	HATU	$EtN(iPr)_2$	DMF	22%
f	*OH*	*HATU*	*Cs_2CO_3*	*CH_2Cl_2*	*85%*
g	OH	HBTU	Cs_2CO_3	CH_2Cl_2	71%

[a] *Abbreviations*: TFFH = tetramethylfluoroformamidinium hexafluorophosphate; HATU = 2-(1′*H*-7′-azabenzotriazol-1′-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; HBTU = 2-(1′*H*-benzotriazol-1′-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate.

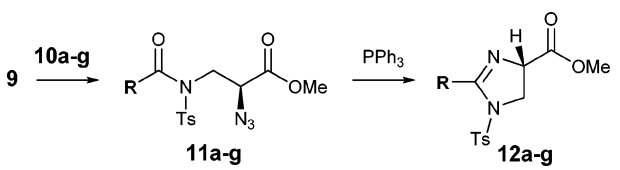
HATU using standard conditions[22] were not very encouraging, and solvent influence was minute (entries d, e). However, after some experimentation it was found that switching from a soluble organic to the insoluble inorganic base Cs_2CO_3 led to surprisingly clean transformations, with excellent yields of amide **11a** (entry f).[23] Interestingly, K_2CO_3 gave inferior results (not shown), indicating that a soluble sulfonamide anion might be involved in the reaction. Switching to the less labile HOBt-derived active ester (entry g) did not improve the outcome of the reaction, showing that both high electrophilicity of the acyl donor as well as sufficient base strength to deprotonate the sulfonamide are important for optimal conversion. Notably, racemization was not observed under these conditions (dr > 97 : 3).

This method was applied to a diverse selection of acyl donors (Table 2). In general, many types of substrates (hindered/unhindered, polar/non-polar, aliphatic/aromatic) performed well and gave the corresponding amides **11** in excellent yields (entries a–e). However, for Ala and Phe (entries f, g) the conversion was unsatisfactory, which may be attributed to premature cleavage of the intermediate active ester by the rather nucleophilic Cs_2CO_3, or formation of unreactive oxazolone intermediates. Gratifyingly, preformed acid fluorides delivered the amides with high efficiency in these cases.

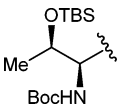
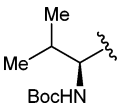
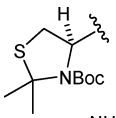
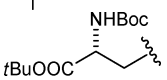
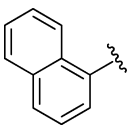
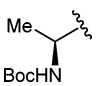
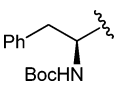
Ring closure of the activated amides **11** to the 2-imidazolines was investigated next. To our delight, initial experiments showed that conversion to the 2-imidazolines **12** was smooth using our previously disclosed conditions.[12c] Imidazoline formation occurred at ambient or elevated temperature in THF with PPh_3, generally with good to excellent yields (Table 2).[23] All compounds could be isolated and were shown to be diastereomerically pure by ^{1}H-NMR. Notably, imidazolines with little steric shielding (**12f**, **12g**) were quite prone to hydrolysis of the activated amidine function, suffering ring opening to a primary sulfonamide. Both acid and wet silica were found to easily trigger this process, but not base. This illustrates that the mild conditions of the aza-Wittig ring closure are ideally suited to directly access even sensitive 2-imidazolines.

In cases of pronounced steric hindrance and low electrophilicity the reaction rates were slow under standard aza-Wittig ring-closure conditions, which was reflected in modest yields

Table 2 Acylations under optimized conditions and aza-Wittig ring closure to 2-imidazolines



11a-g **12a-g**

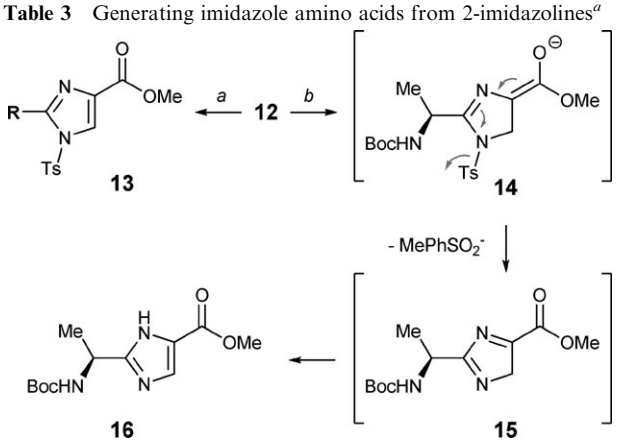
Entry	R =	Method[a]	Yield of **11**	Yield of **12**
a		A	85%	97%[b]
b		A	85%	94%[b]
c		A	85%	46% 80%
d		A	99%	91%[b]
e		A	85%	64% 85%
f		B	97%	91%[b]
g		B	80%	76%[b]

[a] *Reagents and conditions*: A: carboxylic acid, HATU, Cs_2CO_3, CH_2Cl_2, 0 °C; B: acid fluoride, $EtN(iPr)_2$, CH_2Cl_2, 25 °C. [b] PPh_3 (1.5 equiv.), THF, reflux, 2.5–6 h. [c] PPh_3 (1.2 equiv.), 2,6-lutidine, 80 °C, 2–6 h.

(entries c, e). Not unexpectedly, varying the phosphine did not improve this outcome.[12c] In a solvent screen it was found that conducting the ring closure reaction in 2,6-lutidine would lead to better reaction rates and cleaner products (entries c, e). Despite the elevated temperature, epimerizations or eliminations were not observed. The reason of this rather specific solvent effect remains under study. Currently, we speculate that the basic medium neutralizes adventitious acid which otherwise might deactivate the intermediate iminophosphorane **3** by protonation.[24]

Oxidation[12c,14b] to the imidazole could then be smoothly achieved using DBU and $BrCCl_3$ (Table 3).[25] Sterically hindered as well as oxidation prone precursors (*e.g.* **12c**) could be transformed to the imidazole amino acids **13** in very good yields without formation of side products (entries a–c). On the other hand, it would be desirable if oxidation of the ring could be achieved by making use of the high oxidation state of the sulfonyl substituent. First attempts to trigger its elimination with strong bases (KO*t*Bu, DBN, DABCO) were not met with success. To our surprise, treating 2-imidazoline **12f** with an excess of DBU led to clean formation of the imidazole **16** in acceptable yield (entry d).

Table 3 Generating imidazole amino acids from 2-imidazolines[a]



Entry	2-Imidazoline	Method	Product	Yield
a	**12a**	a	**13a**	87%
b	**12c**	a	**13c**	90%
c	**12f**	a	**13f**	76%
d	**12f**	b	**16**	49%

[a] *Reagents and conditions*: (a) **12a**/**12c**/**12f**, DBU (2 equiv.), $BrCCl_3$ (1.1 equiv.), CH_2Cl_2, 30 min; (b) **12f**, DBU (15 equiv.), DMF, 2 h, 0 °C → rt.

The absence of oxygenated side products rules out the involvement of molecular oxygen. We presume that deprotonation leads to a stabilized enolate intermediate such as **14**, which suffers an eliminative loss of methylphenyl sulfinate to yield the putative 5*H*-imidazole **15**. Swift tautomerization to the more stable 1*H* form delivers imidazole **16**. This transformation was not very fast (2 h), however, this may be explained by stereoelectronic factors. The in-plane N–S bond and the conjugated enolate π orbitals probably share insufficient overlap for quick elimination, allowing the enolate then to become oxidatively intercepted when reagents such as $BrCCl_3$ are present.

In conclusion, we have shown that imidazolines can be efficiently formed by intramolecular aza-Wittig ring closures of *N*-acylated azido sulfonamides under essentially neutral conditions, with complete regiocontrol. Substrates were assembled by sulfonamide *N*-acylation, enabling liberal structural variation in the target molecules. Reaction conditions could be found that deliver the target heterocycles with neglible epimerization. It is expected that substrate reactivity can be fine-tuned further by variation of the sulfonamide group. Together with flexible deprotective or non-deprotective tailoring, this method should be helpful for flexible access to key imidazolines and imidazoles in medicinal chemistry, library generation, and target oriented synthesis.

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