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Synthesis of substituted imidazolines by an Ugi/Staudinger/aza-Wittig sequence

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ABSTRACT

A series of 2-(acetamide-2-yl)-imidazolines (II) with 5 points of diversity were prepared by an Ugi-4CR–Staudinger–aza-Wittig-sequence starting from simple azidoalkylamines. The intramolecular aza-Wittig cyclization between the iminophosphane and the tertiary amide of the Ugi product (I) was effected by short microwave irradiation. Competitive cyclization to the secondary amide was not relevant, however, in some cases subsequent formation of the bicyclic *ortho*-amidines (III) was observed.

Introduction

In the last fifteen years the intramolecular aza-Wittig reaction has been established as a versatile and reliable organic transformation for the construction of small and medium sized nitrogen containing heterocycles.[1–9] It is usually conducted under mild conditions (neutral solvent, no acid, base or catalyst), high yielding and possesses good chemoselectivity, which altogether often marks it as the reaction of choice for natural product syntheses.[10–15] A wide variety of carbonyls can be used as substrates: aldehydes, ketones, carboxylic anhydrides,[6] acyl halides,[14] heterocumulenes (ketenes, (thio)isocyanates, CO_2, CS_2),[14,16–18] (thio)ester,[6,19–21] urethanes,[22] and sulfoxides.[6] Amides have long been considered inert under these conditions[23–25] but were found to be reactive if properly activated by electron withdrawing substituents, that is, as imides,[13,24–28] acylureas,[29] or *N*-tosylated amides.[19] Reaction examples for unactivated amides are scarce and usually suffer from inferior yields.[23,30–32]

Multicomponent reactions in general and especially the highly versatile and robust Ugi reaction[33,34] are well-established tools for the generation of screening libraries. In combination with suitable post-condensation modifications (i.e., usually cyclizations which constrain the Ugi product, thereby enhancing its drug properties) they offer quick and easy access to a huge and diverse chemical space of pharmacologically relevant scaffolds.[35–39]

Several examples of MCR-Staudinger–aza-Wittig sequences have been published with both Ugi[30,40–46] and Passerini[47–50] reactions. For combinations of an Ugi reaction followed by (Staudinger)–aza-Wittig cyclization there is only one report for each, the use of an alkyl azide (as opposed to aryl azides yielding benzene annulated products)[42] and the involvement of one of the amide functions generated during the Ugi reaction in the aza-Wittig cyclization.[30]

Based on these findings we envisioned the synthesis of 2-(acetamid-2-yl)-imidazolines with up to five points of diversity by means of an Ugi/Staudinger/aza-Wittig sequence (Scheme 1). Not only would this transformation reduce the peptide character of the primary Ugi product but also enable the rapid synthesis of (dihydro-)imidazolines. This interesting scaffold has found numerous uses, that is, in natural product chemistry,[10] pharmaceutical chemistry,[51] organic synthesis,[19] coordination chemistry, and heterogeneous catalysis.[52] It should be noted that another MCR-based synthesis for this compound class has been published by Hulme et al. using their UDC-strategy (Ugi-DeBOC-Cyclization).[53] In comparison our approach produces a different substitution pattern and has the advantage of neutral cyclization conditions which enable the use of acid labile substrates.

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Results and discussion

Therefore we started with an Ugi reaction between suitably substituted amines, isobutyraldehyde, benzoic acid, and benzyl isocyanide in methanol (1 M) at room temperature (Scheme 2). While 2-bromoethylamine (used as its hydrobromide salt and liberated in situ with 1 equiv of NEt_3) gave no product formation at all, 2-aminoethanol reacted smoothly to the desired product and was isolated after column chromatography in 72% yield. Transformation into the azide was effected with known methods:[54] After activation with MsCl in dry THF and subsequent treatment with an excess of sodium azide at room temperature, **1a** was obtained in 81% yield. Reacting **1a** with 1 equiv of triphenylphosphine in dry toluene led to visible gas evolution and the intermediate iminophosphane, this was then heated in a microwave reactor to 150 °C for 20 min. HPLC/MS analysis indicated (1) that iminophosphane formation was complete after 1 h, and (2) that the aza-Wittig cyclization yielded only a single product without any side products. Analysis by NMR spectroscopy (gHMBC, NOESY) confirmed the imidazoline structure. Crosspeaks were found in the gHMBC spectrum between all of the $-CH_2CH_2-$ protons and only one C(=X)N carbon, and in the NOESY spectrum between one methyl group, the isopropyl-H, and two protons of the ethylene bridge (cf. supporting information). Especially the latter rules out the aminopiperazine structure as the respective groups are placed at opposite sides of the core cycle. Furthermore these findings are consistent with the observation of Zhong et al. who found that only the tertiary amide of an Ugi product reacts in an intramolecular aza-Wittig cyclization.[30]

With these promising results we turned to examine the reaction conditions (Table 1). First several runs at different temperatures for 10 min were performed: unsurprisingly, no reaction took place at lower temperatures. At 110 °C the conversion started, at 130 °C the reaction was nearly complete, and at 150 °C no more starting material could be detected. Given the fact that 10 min. at 130 °C led to near complete conversion we assumed that the reaction is probably finished within a minute at 150 °C. Nonetheless we did not reduce the reaction time further for two reasons: first to keep a safety margin for substituents that do not perform as well as those in this single example, and second because we did not observe any side product formation or other adverse effects at this temperature.

Table 1
Evaluation of reaction conditions

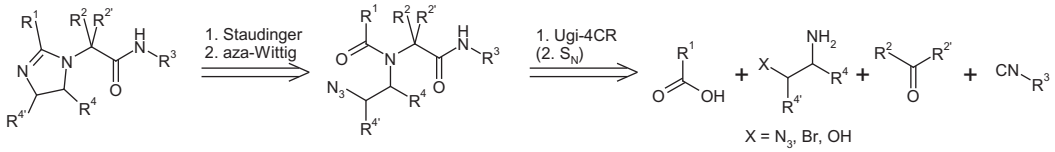
Entry	Conditions	Result[a]
1	50 °C	No reaction
2	80 °C	No reaction
3	110 °C	Conversion <10%
4	130 °C	Conversion >95%
5	150 °C	Clean, complete conversion
6	Reflux, 1 h	Clean, complete conversion
7	Ambient atmosphere	Slight side product formation
8	Non-dry toluene	Slight side product formation
9	Resin bound PPh_3 (1 equiv)	Longer reaction time for iminophosphane formation, clean, complete conversion

Reaction conditions unless noted otherwise: 1 equiv PPh_3, dry toluene, nitrogen atmosphere, microwave, 150 °C, 10 min unless stated otherwise.
[a] Estimated by HPLC/MS.

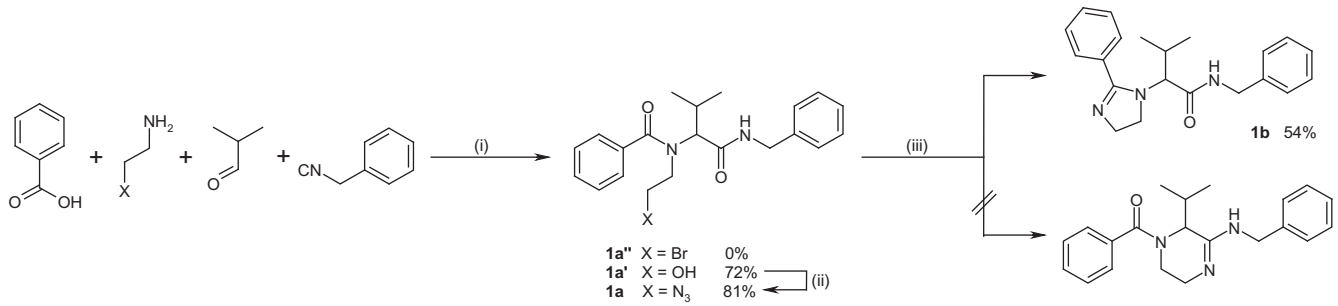
The reaction can be run with conventional heating, too (Table 1, entry 6). Exclusion of air and moisture is not strictly necessary but advantageous as far as side product formation is concerned (entries 7 and 8).

When triphenylphosphine is replaced with its polymer bound equivalent (1.2–1.5 mmol/g, crosslinked with 1% divinylbenzene, 200–400 mesh) the reaction time of the Staudinger reaction is significantly increased but in return the pure product can be obtained by simple filtration and washing with dichloromethane in near quantitative yield.

With this optimized protocol at hand we started synthesizing a small library to evaluate the influence of the different substituents. In order to further simplify the synthesis we switched from 2-aminoethanol to 2-azidoethylamine which can be easily prepared in multigram quantities in one step from cheap 2-bromoethylamine.[55] Substituted azidoethylamines were synthesized from the corresponding amino alcohols according to Wannaporn et al.[54] The Ugi reactions with these azidoalkylamines were noticeably exothermic and surprisingly fast—in most cases the reaction was finished in less than 5 min, yet clean and high yielding. The yield primarily depends on the isocyanide (benzyl isocyanide gave the



Scheme 1. Imidazoline synthesis by an Ugi–Staudinger–aza-Wittig sequence.



Scheme 2. Reagents and conditions: (i) (MeOH), rt, 22 h, 72%; (ii) (a) MsCl, NEt_3, (dry THF), rt, overnight, (b) NaN_3, (dry DMF), rt, 6 h, 81%; (iii) (a) PPh_3, (dry toluene), rt, 2 h, (b) microwave, 150 °C, 20 min, 54%.

best results of our set). The relatively low yield for entry 16 can be attributed to the fact that this amine had to be used as its hydrochloride salt and was liberated in situ with 1 equiv of triethylamine. Since Ugi reactions perform best in acidic and not well in basic medium,[35] this is not ideal, but generation of the free base prior to the Ugi reaction leads to no product formation at all. In two instances the two diastereomers could be separated (entries 15 and 16).

The cyclization proved to be very reliable, producing the desired imidazolines in often quantitative amount. In some cases an additional purification by column chromatography was required which is reflected in reduced yields (entries 7, 12, 13). Both electron rich and poor aromatic substituents are tolerated for R^1 (entries 2–5). For the cyclization of **6a** and **7a** two scouting experiments were performed with normal triphenylphosphine to ensure that the reaction time is sufficient. While **6a** was completely converted within the given 10 min, **7a** required 30 min. Both reactions show in their HPL chromatograms some side product formation. In the course of the subsequent purification by column chromatography **6b** hydrolyzed completely. When the experiment was repeated, we noticed that (1) the product obtained was actually a 1/1 mixture of amidine **6b** and *ortho*-amidine **6c** (vide infra), and (2) that **6b** was converted for the most part upon standing in $CDCl_3$ at room temperature to **6c** within one day (Fig. 1). Further attempts to isolate **6c** were unfruitful due to rapid hydrolysis of the product.

The carbonyl residues R^2, $R^{2'}$ have no adverse influence either as long as at least one of them is an H (entries 8 and 9). For geminal substitutions (entry 10) exerting a strong Thorpe–Ingold effect for the second cyclization, the formation to the *ortho*-amidine **10c** occurred in varying amounts (50% and 17% NMR yield in two separate runs); that is, obviously the rate of equilibration depends on subtle influences like pH. Substitution at the azide side chain is tolerated in both α- and β-positions. Unlike the α-carbon which retains its stereochemical configuration during the aza-Wittig cyclization even with R^4 = Ph (entry 15) the β-carbon is configurationally not stable: Both diastereomers of **16a** racemized partially giving mixtures with a de of 1/3. One remarkable difference in the cyclization of the two diastereomers of **15a** is that *d1* reacted quantitatively without any side products or *o*-amidine formation whereas *d2* produced not only less **15b** but also a significant amount of **15c**. In general the amount of *o*-amidine formed seems to be dependent on the size of R^1 (steric shielding of the amidine), $R^2/R^{2'}$ (Thorpe–Ingold effect), and the steric repulsion of $R^{4/4'}$ and R^2 (Scheme 3 and Table 2).

The *o*-amidines were identified and characterized by NMR-spectroscopy. In the ^1H spectrum of **6c**, the signals of the benzylic protons exhibit only a geminal coupling of ^2J = 14.6 Hz and are more separated than the dd correlating to the NHCH_2Ph group of the aza-Wittig product. This indicates a reaction of the amid-NH of **6a** with concomitant conformational fixation. Additionally, there is a new singlet at 5.20 ppm which is linked to a carbon-signal at 91.0 ppm; both values are similar to what is expected for a C*H*NN′N″ moiety and described in the only publication we have found for this type of structure.[56] Further another new, broad singlet for the CHN*H*N′N″ shows at 2.1 ppm. This signal shows coupling in a NOESY experiment to the imidazoline –CH_2-through spin diffusion (cross peak with the same phase as the diagonal peaks). Isolation of the *o*-amidines was attempted but failed due to hydrolysis of the product (**6c**), re-equilibration (**10b**/**c**), or insufficient yield (**15c**).

Attempts to expand this methodology to the synthesis of larger ring cyclic amidines were unsuccessful (Scheme 4). 3-Azidopropylamine was prepared in analogy to 2-azidoethylamine[55] and reacted as smoothly in the Ugi reaction. Iminophosphorane formation was unproblematic but the cyclization yielded only a mixture of (eventually) hydrolyzed or otherwise deteriorated products.

Finally we examined the synthesis of amidines with different substitution patterns by placing the azido group at other residues of the Ugi product (scheme 5). Unfortunately all attempts were met with failure. Chloroacetone (scheme 5, (1)) could be reacted with 2-methoxyethylamine, benzoic acid, and benzyl isocyanide in an Ugi reaction but reacted during the reaction to give i.a. **18a**

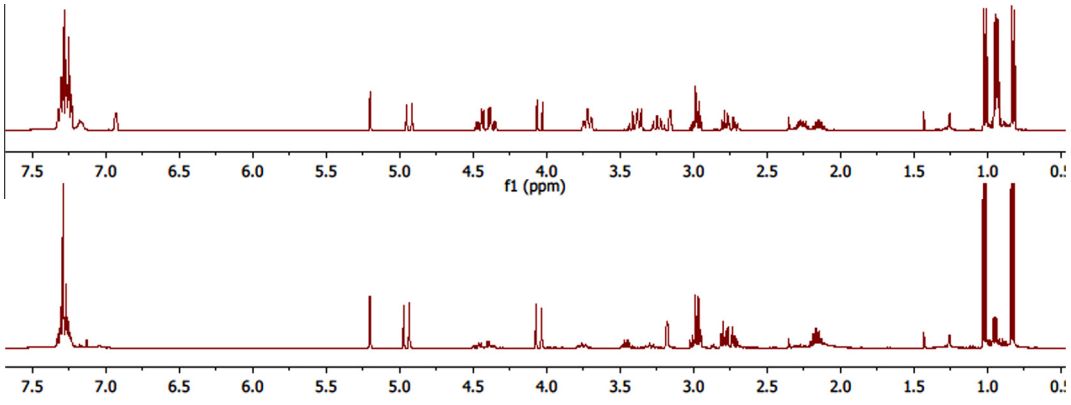
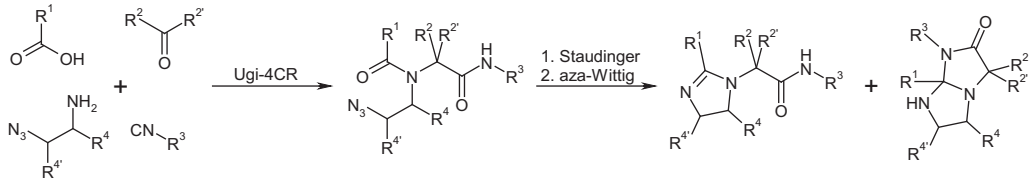


Figure 1. ^1H NMR spectra of the cyclization products of **6a**. Top: directly after the cyclization: **6b**/**6c** = 3/2. Bottom: same sample after standing 24 h at room temperature: **6b**/**6c** = 1/5.

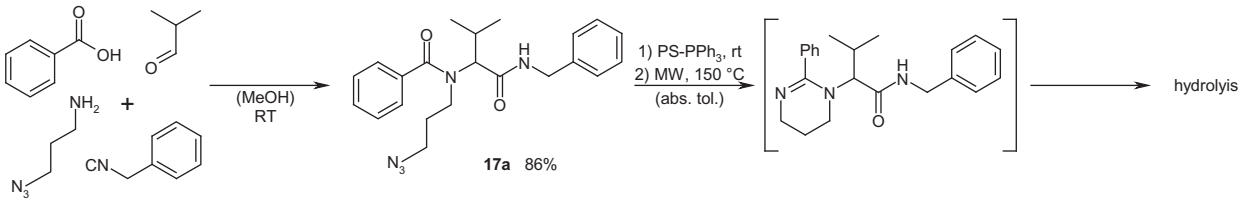


Scheme 3. General reaction scheme.

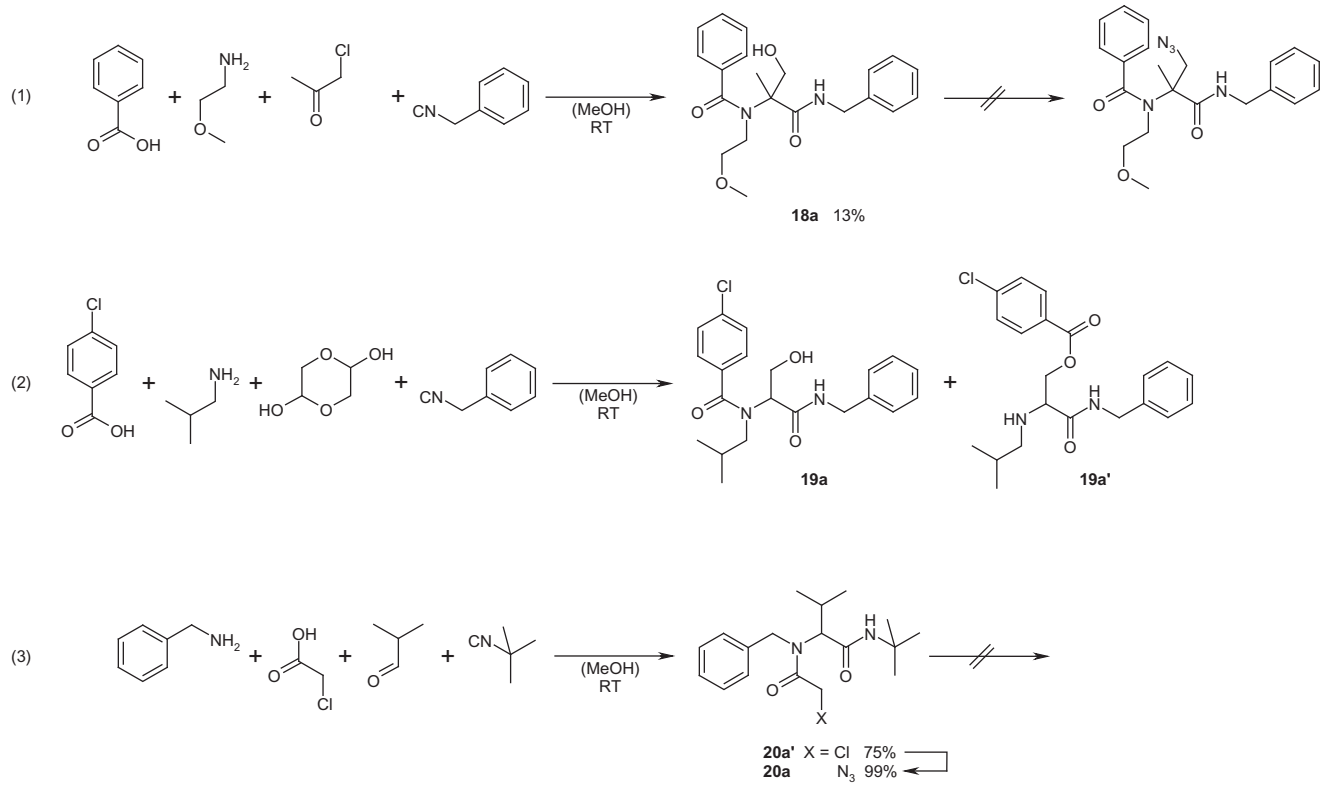
Table 2
Compounds synthesized by Ugi–Staudinger–aza-Wittig-sequence

Entry	R^1	R^2, $R^{2'}$	R^3	R^4, $R^{4'}$	Ugi product	Yield[a]	Imidazoline	Yield[a]	*o*-Amidine	Yield[b]
1	Ph	^{i}Pr, H	Bn	H, H	**1a**	90%	**1b**	99%	**1c**	0%
2	4-Cl-Ph	^{i}Pr, H	Bn	H, H	**2a**	85%	**2b**	97%	**2c**	< 2%
3	4-Meo-Ph	^{i}Pr, H	Bn	H, H	**3a**	92%	**3b**	99%	**3c**	0%
4	2-Thiophenyl	^{i}Pr, H	Bn	H, H	**4a**	84%	**4b**	69%	**4c**	0%
5	4-Pyridyl	^{i}Pr, H	Bn	H, H	**5a**	90%	**5b**	92%	**5c**	7%
6	H	^{i}Pr, H	Bn	H, H	**6a**	79%	**6b**	0%	**6c**	80%.
7	Me	^{i}Pr, H	Bn	H, H	**7a**	87%	**7b**[c]	60%	**7c**[c]	4%
8	Ph	H, H	Bn	H, H	**8a**	89%	**8b**	99%	**8c**	0%
9	Ph	Ph, H	Bn	H, H	**9a**	85%	**9b**	99%	**9c**	0%
10	Ph	Me, Me	Bn	H, H	**10a**	87%	**10b**	0% (50–85%)[b]	**10c**	15–50%
11	Ph	^{i}Pr, H	Ph	H, H	**11a**	64%	**11b**	99%	**11c**	0%
12	Ph	^{i}Pr, H	^{t}Bu	H, H	**12a**	60%	**12b**	79%	**12c**	7%
13	Ph	^{i}Pr, H	$-(CH_2)_2OMe$	H, H	**13a**	59%	**13b**	72%	**13c**	10%
14	Ph	^{i}Pr, H	Bn	Bn, H	**14a**	93%	**14b**	93%	**14c**	5%
15	Ph	^{i}Pr, H	Bn	Ph, H	**15a**	*d1*: 54% *d2*: 36%	**15b**	*d1*: 99% *d2*: 36%[d]	**15c**	*d1*: 0% *d2*: 25%
16	Ph	^{i}Pr, H	Bn	H, Me	**16a**	*d1*: 21% *d2*: 22%	**16b**	*d1*: 74% *d2*: 97%	**16c**	*d1*: 0% *d2*: 0%

[a] Isolated yield.
[b] Determined by ^{1}H NMR analysis of the reaction mixture.
[c] Reaction time: 30 min.
[d] TFA salt.



Scheme 4. Attempted tetrahydropyrimidine synthesis.



Scheme 5. Permutations examined.

in a low yield. Activation with mesyl chloride and subsequent treatment with sodium azide in dry DMF at 50 °C led to complete degradation of the starting material within 5 h. We reasoned that this might be attributed to the quaternary carbon next to the leaving group. Therefore we tried to substitute chloroacetone with glycolaldehyde. The Ugi reaction with its dimer yielded a mixture of the regular Ugi-4CR product **19a** and an isomer **19a′**, resulting from an alternative Mumm-type rearrangement with the alcohol as the internal nucleophile. The mixture proved inseparable by standard column chromatography and was therefore abandoned.[57,58] As last permutation we tried to place the azide at the acid derived side chain. Ugi reaction with chloroacetic acid gave **20a** which was easily converted into azide **20a′**. Treatment with triphenylphosphine led to the corresponding iminophosphane which refused to cyclize. Even at 180 °C for 1 h neither traces of the desired product nor any degradation products were formed. Seemingly the steric hindrance with an isopropyl and a *tert*-butyl group α and α′ to the carbonyl, respectively, are sterically too demanding.

Conclusion

In summary we have developed a novel route to substituted 2-(acetamid-2-yl)-imidazolines with up to five points of diversity by an Ugi–Staudinger–aza-Wittig sequence. This 3-step procedure offers a quick and high yielding (up to 91% overall yield) entry to this important structural class. In some cases intramolecular cyclization to the corresponding *ortho*-amidines was observed.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.01.043.

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