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

Sebastian J. Welsch [a,*], Michael Umkehrer [b], Cedric Kalinski [b], Günther Ross [b], Christoph Burdack [b], Jürgen Kolb [b], Martina Wild [b], Anja Ehrlich [a], Ludger A. Wessjohann [a]

[a] Leibniz-Institut für Pflanzenbiochemie, Weinberg 3, 06120 Halle a. d. Saale, Germany
[b] Priaxon AG, Rupert-Mayer-Str. 46, 81379 Muenchen, Germany

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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.

* Corresponding author.
E-mail addresses: Sebastian.Welsch@student.uni-halle.de (S.J. Welsch), Ludger.Wessjohann@ipb-halle.de (L.A. Wessjohann).

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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

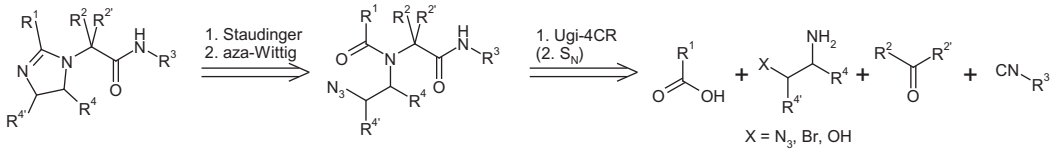
Entry	Conditions	Result[a]
1	50 °C	No reaction
2	80 °C	No reaction
3	110 °C	Conversion <10%
4	130 °C	Conversion >95%
5	150 °C	Clean, complete conversion
6	Reflux, 1 h	Clean, complete conversion
7	Ambient atmosphere	Slight side product formation
8	Non-dry toluene	Slight side product formation
9	Resin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

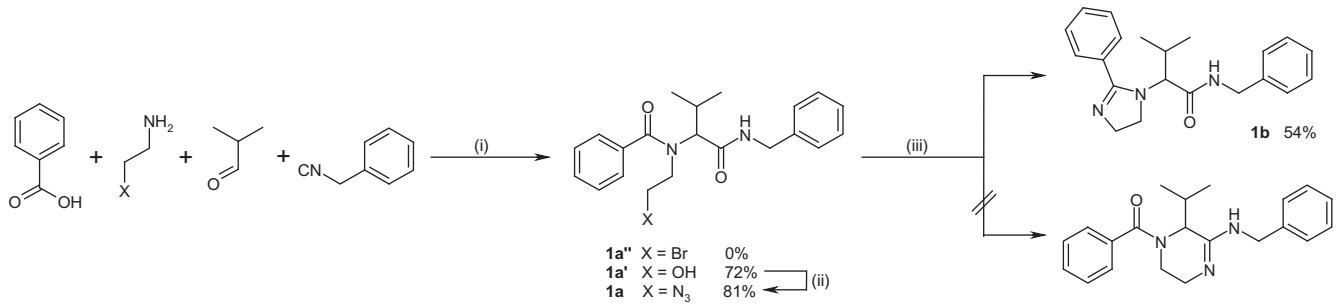
The reaction can be run with conventional heating, too (Table 1, entry 6). Exclusion of air and moisture is not strictly necessary but advantageous as far as side product formation is concerned (entries 7 and 8).

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%.