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Synthesis of substituted fused pyridines, pyrazines and pyrimidines by sequential Ugi/inverse electron demand Diels–Alder transformations

Irini Akritopoulou-Zanze *, Ying Wang, Hongyu Zhao, Stevan W. Djuric

Scaffold Oriented Synthesis, Abbott Laboratories, R4CP, AP10, 100 Abbott Park Road, Abbott Park, IL 60064-6099, USA

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ABSTRACT

The synthesis of all four regioisomers of fused pyrrolidino-pyridines in a one-pot two-step sequential Ugi-inverse electron demand Diels–Alder reaction is described. Fused pyrrolidino-pyrazines, pyrrolidino-pyrimidines and azepinone pyridines can also be obtained in consecutive synthetic sequences.

1. Introduction

Isocyanide-based multicomponent reactions (IMCRs) have gained a prominent place in organic synthesis by providing access to highly functionalized structures in a facile and straightforward manner.[1] Furthermore, these reactions are often combined with additional transformations to yield products not easily obtained by other synthetic methods.[2]

As part of our group's efforts to explore synthetic methodologies to access unique scaffolds[3] or pharmaceutically related heterocycles,[4] we became interested in combining the Ugi reaction with an inverse electron demand Diels–Alder reaction.[5] The reaction sequence was expected to yield pyridines, heterocycles commonly found in drugs.[4] The first Ugi/Diels–Alder combination was reported 10 years ago by Paulvannan.[6] Since then numerous groups have utilized this synthetic sequence in various forms.[7] However, to our knowledge there are no accounts of incorporating electron-deficient azadiene moieties into the Ugi inputs in order to effect subsequent inverse electron demand Diels–Alder reactions.

We initiated our studies by employing 1,2,4 triazine carboxylic acid **1**[8] (Schemes 1 and 2) and propargyl amine as the two Ugi components poised for a Diels–Alder reaction (Fig. 1). We have found that the Diels–Alder product **1a** was cleanly produced in 32% yield and its structure was verified by X-ray. No other identifiable products were observed or isolated.

Table 1 summarizes the results of additional examples employing different triazine[9] (Scheme 3) and triple bond components. As expected the use of a double bond input (Table 1, entry 4) resulted in the same product as the one in entry 2, Table 1 via air oxidation of the corresponding Diels–Alder intermediate. When triazinoaldehydes were employed, higher temperatures were required for complete conversion to the final products.

It is noteworthy that, even though the products were obtained in moderate yields, by varying the inputs of the Ugi reaction all four regioisomers of fused pyrrolidino-pyridines could be obtained in a one-pot procedure.

Although the formation of five-membered pyrrolidino-pyridines was accomplished at lower temperatures, the formation of larger rings proved to be problematic. In most cases the Ugi adducts were isolated in low yields and subsequent cycloaddition

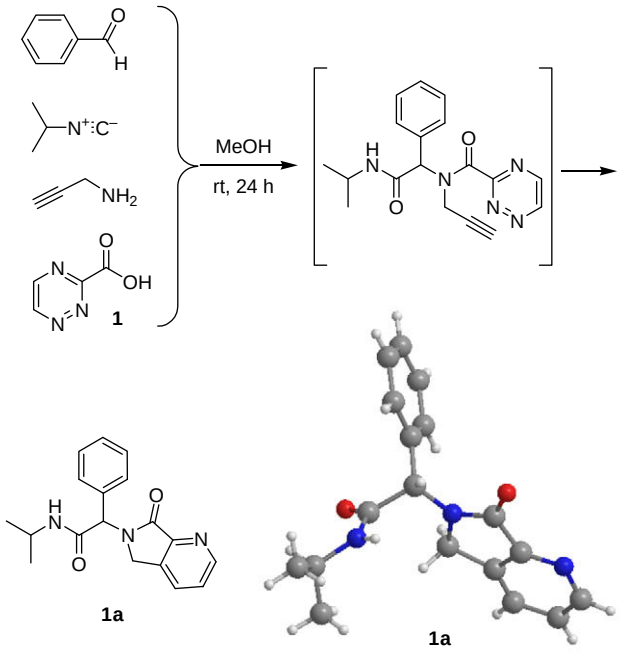

Figure 1. One-pot Ugi/inverse electron demand Diels–Alder reaction and X-ray of the product.

* Corresponding author. Tel.: +1 847 937 5006; fax: +1 847 935 0310.
E-mail address: irini.zanze@abbott.com (I. Akritopoulou-Zanze).

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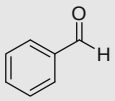
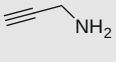
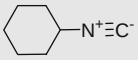
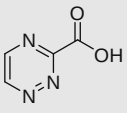
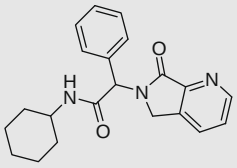
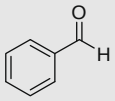
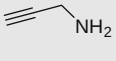
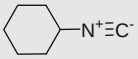
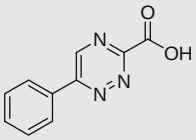
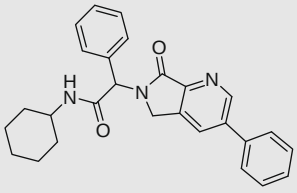
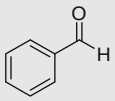
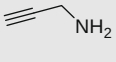
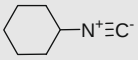
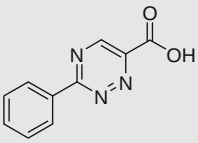
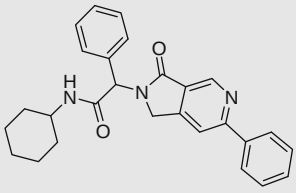
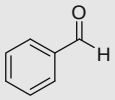
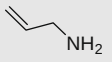
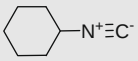
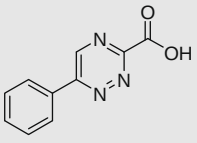
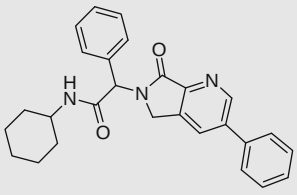
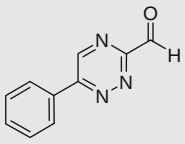
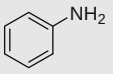
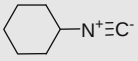
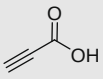
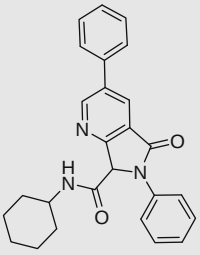
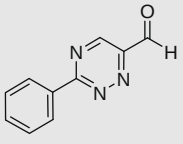
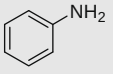
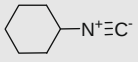
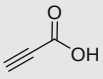
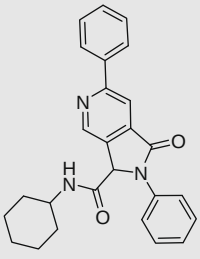
Table 1
One-pot sequential Ugi/Inverse electron demand Diels–Alder reactions

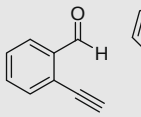
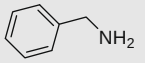
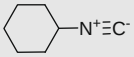
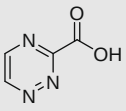
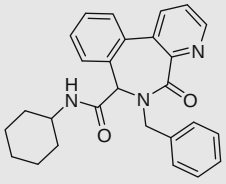
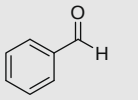
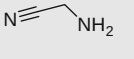
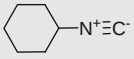
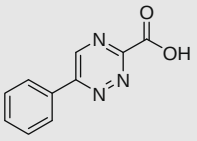
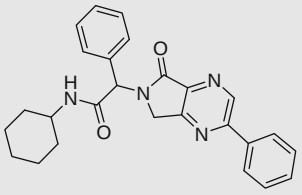
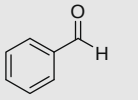
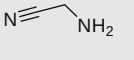
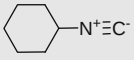
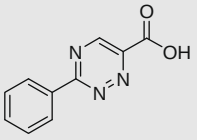
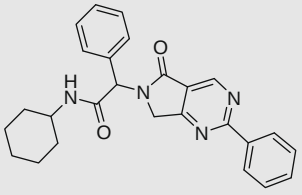
	Aldehyde	Amine	Isocyanide	Acid	Isolated product	Time, temp	Yield[a] (%)
1						3 h, 25 °C	47
2						3 h, 50 °C	34
3						3 h, 50 °C	31
4						3 h, 50 °C	25
5						1 h, 80 °C	27
6						1 h, 60 °C	48

[a] Isolated yield after silica-gel column chromatography. Reactions were carried out in MeOH.

reactions resulted only in decomposition. We were, however, able to effect the Diels–Alder transformation shown in entry 1 in Table 2 by heating the isolated Ugi adduct at 130 °C to obtain a novel fused azepinone pyridine.

In addition to triple and double bonds, nitrile dienophiles have also been used for inverse electron demand Diels–Alder reactions.[10] The Ugi reactions of 2-aminoacetonitrile with 1,2,4 triazino acids proceeded in moderate yields to provide the Ugi adducts. The subsequent Diels–Alder reaction occurred at elevated temperatures following a microwave protocol developed for related systems.[11] Thus heating the Ugi adducts in chlorobenzene at 220 °C for 3 h in a Biotage Initiator microwave resulted in complete conversion to

Table 2
Two-step sequential Ugi/Inverse electron demand Diels–Alder reactions

	Aldehyde	Amine	Isocyanide	Acid	Ugi Yield[a] (%)	Diels–Alder product	Diels–Alder yield[b] (%)
1					50		25[c]
2					32		43
3					76		46

[a] Isolated yield of the Ugi step carried out in MeOH, rt, 4–24 h.
[b] Isolated yield of the Diels–Alder step carried out in chlorobenzene, 220 °C, MW, 3 h.
[c] Chlorobenzene, 130 °C, 48 h.

the corresponding pyrazines and pyrimidines. Lower temperatures and shorter periods of time resulted only in partial conversions.

2. Conclusions

In conclusion, we have developed a multicomponent / inverse electron demand Diels–Alder reaction sequence,[12] that provided access to fused pyrrolidino-pyridines, pyrrolidino-pyrazines, pyrrolidino-pyrimidines and azepinone pyridines. In the case of pyrrolidino-pyridines the transformation afforded a convenient approach to access all four regioisomers in a one-pot procedure.

Acknowledgements

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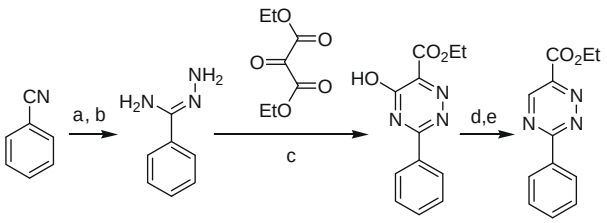
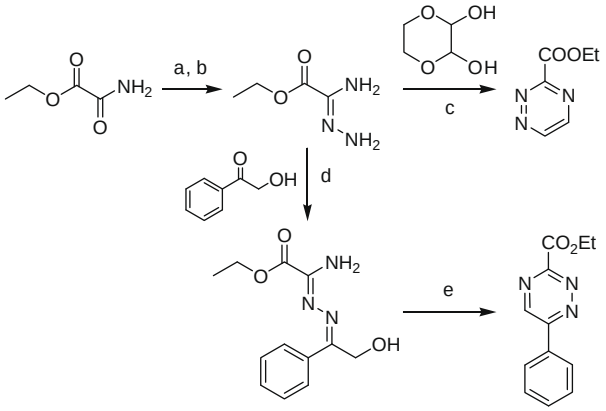
8. Triazine carboxylic acids were isolated as the potassium salts from the corresponding esters (Schemes 1 and 2) upon treatment with KOH in MeOH. Prior to the Ugi reactions the salts were dissolved in MeOH, acidified with 1 equiv of 4 N HCl in dioxane and used as methanolic solutions for the Ugi step.

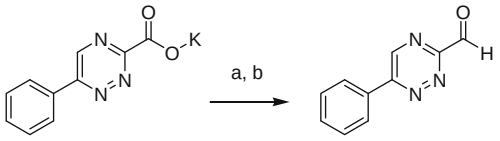


Scheme 1. Reagents and conditions: (a) HCl (gas), MeOH, −78 °C to rt, 24 h; (b) $N_2H_4{\cdot}H_2O$, EtOH, 0 °C 48 h, 74% in two steps; (c) EtOH, 0 °C to rt, 16 h, reflux 6 h, 40%; (d) PCl_5, toluene, reflux, 1 h, 70%; (e) H_2, Pd/C, Et_3N, rt, 11/2 h, 22%.



Scheme 2. Reagents and conditions: (a) Lawesson's reagent, THF, reflux, 2 h, 86%; (b) $N2H_4{\cdot}H_2O$, EtOH, rt, 1/2 h, 83%; (c) AcOH, EtOH, THF, -78 °C 1/2 h then Et_3N, rt, 24 h; (d) THF, 0 °C to reflux, 24 h, (e) MnO_2, toluene, rt to reflux, 17 h, 25% in two steps.

9. Triazine aldehydes were prepared from the corresponding carboxylic acid potassium salts (Scheme 3).



Scheme 3. (a) BnBr, DMF, 80 °C, 16 h; (b) DIBAL-H, CH_2Cl_2, −78 °C, 1/2 h 20% in two steps.

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12. Representative experimental procedure for example 1 given in Table 1. Potassium 1,2,4-triazine-3-carboxylate (100 mg, 0.613 mmol) in MeOH (0.5 mL) was treated with 4 N HCl in dioxane (0.153 mL, 0.613 mmol) for 5 min and the suspension was added to a solution of benzaldehyde (0.065 mL, 0.613 mmol), prop-2-yn-1-amine (0.039 mL, 0.613 mmol) and isocyanocyclohexane (0.076 mL, 0.613 mmol) in MeOH (2 mL). The mixture was stirred at room temperature for 3 h. The solvent was evaporated and the crude material was purified by silica gel chromatography eluting with 30–100% ethyl acetate/hexanes to obtain the product. (100 mg, 47% yield). ^{1}H NMR (500 MHz, DMSO) δ 8.72 (dd, J = 1.1, 4.7, 1H), 8.40 (d, J = 7.7, 1H), 8.00 (dd, J = 0.9, 7.7, 1H), 7.55 (dd, J = 4.8, 7.7, 1H), 7.43 (dd, J = 3.8, 10.8, 2H), 7.39–7.34 (m, 1H), 7.34–7.29 (m, 2H), 6.09 (s, 1H), 4.82 (d, J = 18.1, 1H), 3.94 (d, J = 18.1, 1H), 3.70–3.53 (m, 1H), 1.82–1.72 (m, 2H), 1.72–1.61 (m, 2H), 1.61–1.48 (m, 1H), 1.34–1.17 (m, 3H), 1.17–1.06 (m, 2H). MS (ESI+) m/z 350 $(M+H)^+$.