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ARTICLE

One-pot and catalyst-free synthesis of pyrroloquinolinediones and quinolinedicarboxylates†

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A method for catalyst-free synthesis of pyrroloquinolinediones and quinolinedicarboxylates is developed through a one-pot synthesis involving denitrogenation of azide, benzisoxazole formation, aza-Diels-Alder cycloaddition, and dehydrative aromatization. Only a stoichiometric amount of N_2 and H_2O is produced as byproducts. A comprehensive green chemistry metrics analysis indicated that this method is much more efficient and greener than two reported methods for the synthesis of pyrroloquinolinediones.

Introduction

Quinoline is a privileged scaffold which could be found in a wide range of natural products, bioactive compounds, fluorescent and phosphorescent probe molecules, and ligands for catalysis.[1] Pyrroloquinolines and pyrroloquinolinediones are important derivatives of quinolines. Compounds from these two subfamilies of quinolines, such as luotonin A,[2] camptothecin,[3] mappicine,[4] and caspase-3 inhibitors,[5] have significant biological activities (Figure 1). Cyclization and cycloaddition reactions of 2-aminobenzaldehyde- and maleimide-related compounds are two common methods for the synthesis of pyrroloquinolinediones (Scheme 1).[6] The reported methods are multistep syntheses and usually require metal catalysts. Introduced in this paper is a catalyst-free and one-pot synthesis of pyrroloquinolinediones from readily available azidobenzaldehydes and maleimides. The method is also applicable for the synthesis of quinolinedicarboxylates.

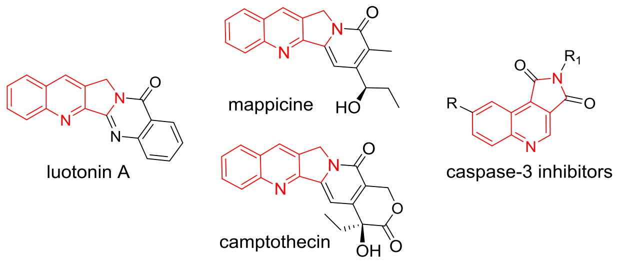
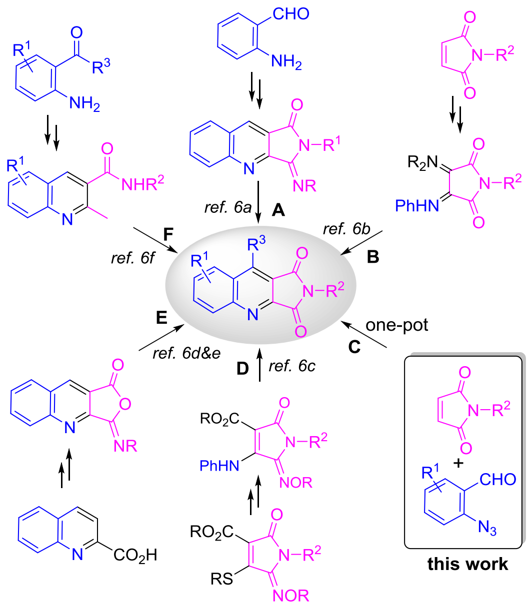


Fig. 1 Bioactive pyrroloquinolines and pyrroloquinolinediones.



Scheme 1 Processes A-F for the synthesis of pyrroloquinolinediones.

2-Azidobenzaldehydes are a feasible synthon for diverse nitrogen-heterocyclic compounds including benzisoxazoles and quinolines.[7] As part of our recent effort on the development of multicomponent reaction-based synthesis of polycyclic compounds,[8] we have introduced a number of [3+2] cycloaddition-initiated synthesis using substituted 2-azidobenzaldehydes as starting materials (Scheme 2).[9] After the [3+2] cycloaddition, the azido group was used for another [3+2] cycloaddition or reduced to amino group for further derivatization to form scaffolds **I-III**. In this work, 2-azidobenzaldehydes are employed as a precursor for aza-Diels-Alder cycloadditions to form pyrroloquinolinediones **1** and quinolinedicarboxylates **2**.

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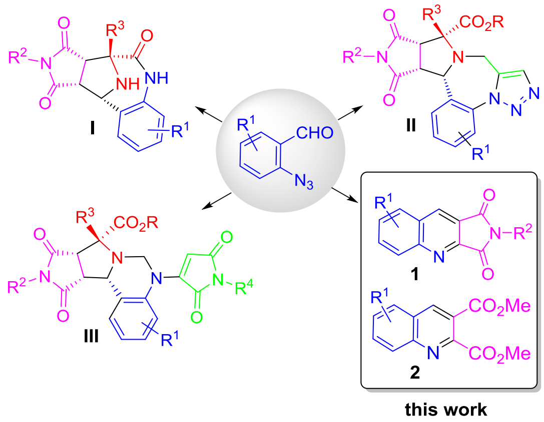
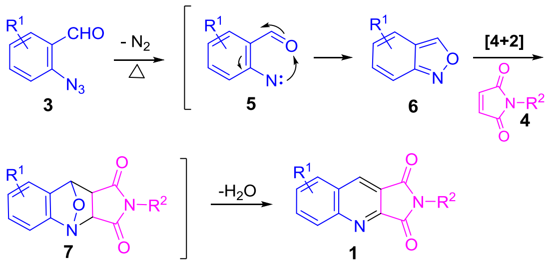


Scheme 2 2-Azidobenzaldehyde-based synthesis of heterocycles.

Results and Discussion

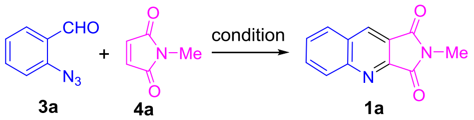
Literature search revealed that benzisoxazoles **6** generated from denitrogenation of 2-azidobenzaldehydes **3** could be used as precursors for aza-Diels-Alder cycloaddition[10] or metal-catalyzed [4+2] annulation reactions.[11] Based on this information, we proposed a one-pot synthesis of pyrroloquinolinediones **1** involving thermal denitrogenation of 2-azidobenzaldehydes **3,** cyclization of nitrenes **5,** aza-Diels-Alder reaction of benzisoxazoles **6** with maleimides **4,** and dehydrative aromatization of **7** (Scheme 3).



Scheme 3. Proposed one-pot synthesis of pyrroloquinolinediones **1.**

A clean conversion of 2-azidobenzaldehyde **3a** to benzisoxazole **6a** under microwave heating at 115 °C for 20 min was observed by ^{1}H-NMR analysis (see SupInf). We then carried out a model reaction of 2-azidobenzaldehyde **3a** and *N*-methyl maleimide **4a** to establish the reaction conditions for the one-pot synthesis. After screening a series of metal catalysts including CuI and AlCl$_3$, we found that none of these catalysts gave greater than 40% yield of product **1a** (Table 1, entries 1&2). A reaction without metal catalyst but using *N,N*-diisopropylethylamine (DIPEA) as a base gave **1a** in 88% yield (entry 3). A reaction without using a base gave **1a** in 71% yield (entry 4). It was found that microwave heating significantly reduced the reaction time (entries 5-9). The optimized condition was to conduct the catalyst-free reaction without a base, and using 1:1.1 of **3a** and **4a** in MeCN under microwave heating, at 115 °C for 35 min, which afforded pyrroloquinolinedione **1a** in 89% isolated yield (entry 6).

Table 1. Development of reaction conditions[a]

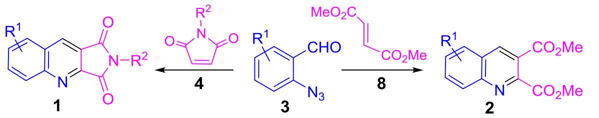


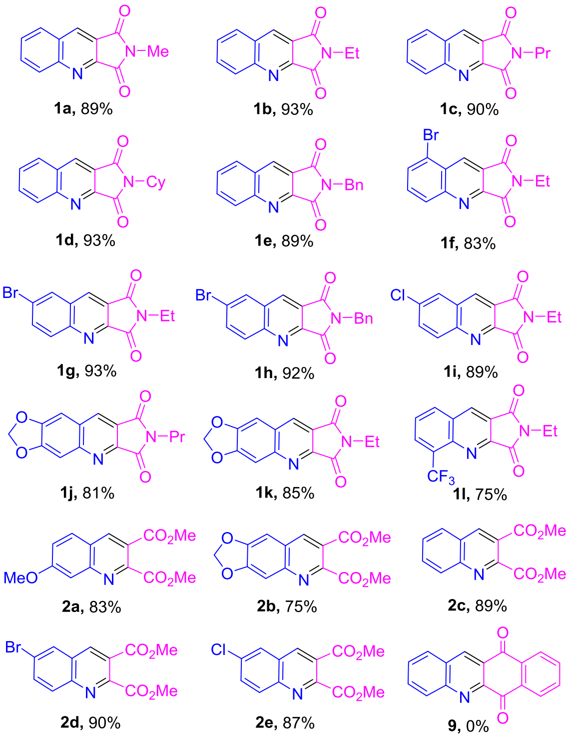
Entry	Catalyst (equiv)	Temp (°C)	Solvent	Time	1a (%)[b]
1	CuI (0.1)	85	CH$_3$CN	12 h	39
2	AlCl$_3$ (0.3)	85	CH$_3$CN	3 h	ND
3	DIPEA (1.0)	85	CH$_3$CN	12 h	88
4	-	85	CH$_3$CN	12 h	71
5	DIPEA (1.0)	115 (μw)	CH$_3$CN	35 min	90
6	**-**	**115 (μw)**	**CH$_3$CN**	**35 min**	**92 (89)**
7	-	150 (μw)	CH$_3$CN	35 min	92
8	-	115 (μw)	EtOH	35 min	15
9	-	115 (μw)	toluene	35 min	71

[a] 1:1.1 of **3a**:**4a**. [b] Detected by LC, isolated yield in parenthesis.

With the optimized reaction conditions in hand, we carried out reactions with a series of 2-azidobenzaldehydes **3** and maleimides **4**

Table 2. One-pot synthesis of pyrroloquinolinediones **1** and quinolinedicarboxylates **2.**[a]





1a, 89% **1b**, 93% **1c**, 90%

1d, 93% **1e**, 89% **1f**, 83%

1g, 93% **1h**, 92% **1i**, 89%

1j, 81% **1k**, 85% **1l**, 75%

2a, 83% **2b**, 75% **2c**, 89%

2d, 90% **2e**, 87% **9**, 0%

[a] Conditions: 1:1.1 of **3**:**4** (or **8**) in MeCN, μw heating at 115 °C for 35 min, isolated yields

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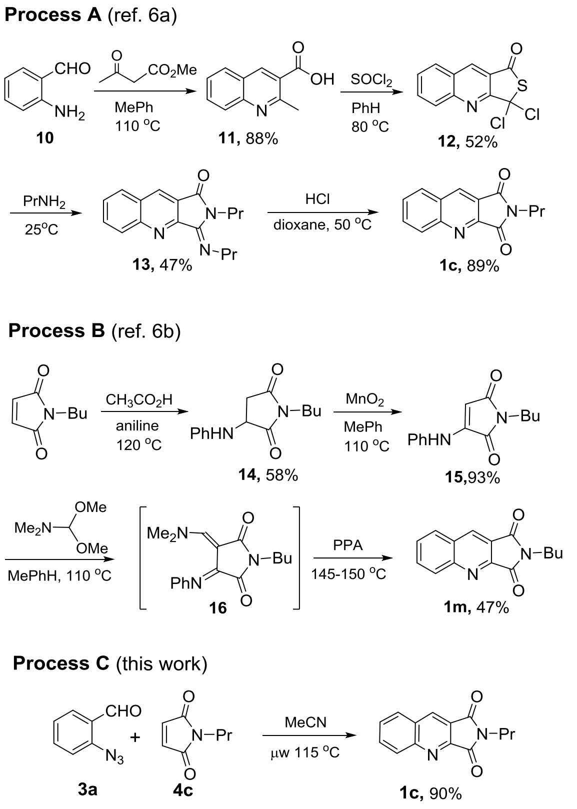
for the synthesis of pyrroloquinolinediones **1** bearing different R^1 and R^2 groups (Table 2). The isolated yields of products **1a-l** are in the range of 75-93%. By replacing maleimides **4** with dimethyl fumarate **8** (*E*-isomer), reactions produced quinolinedicarboxylates **2a-e** in 75-90% yields.[12] A similar result was obtained using dimethyl maleate (*Z*-isomer) for the synthesis of **2a**. A reaction with 1,4-naphthoquinone didn't give product **9.**

Evaluation of green chemistry credentials of the one-pot synthesis (Process C) for pyrroloquinolinediones and comparison it with two literature methods highlighted in Scheme 4 (Processes A and B) was done by performing a series of green metrics calculations[13,14] (see SupInf for the definition of different metrics and related calculations). Since 2-aminobenzaldehyde and maleimide used in the Processes A and B are closely related to the starting materials used in the Process C (Scheme 4), which make the comparison more meaningful. Process A is a four-step synthesis starting from 2-aminobenzaldehyde.[6f] Process B starting from *N*-butyl maleimide has an intermediate **16** which was not isolated, it was treated as a three-step synthesis for calculation.[6b] First of all, atom economy (AE) and atom efficiency (AEf) were calculated to estimate the amount of the reactants that will remain in the product. But these metrics ignores the inorganic reagents as well as solvents that are not incorporated into the final product. Moreover, significant stoichiometric excess is also not considered in AE and AEf. Therefore, carbon efficiency (CE), reaction mass efficiency (RME), overall efficiency (OE), process mass intensity (PMI), solvent intensity (SI), water intensity (WI), E-factor (E) and mass productivity (MP) were also calculated (Tables 3 and 4).



Scheme 4. Processes A-C for the synthesis of pyrroloquinolinediones.

The AE for Process C is less than 100% due to the formation of H_2O and N_2 as by-products (Table 3). However, it has inherited high atom economy (83.92%) and atom efficiency (75.53%) which is significantly better than those for Process A (57.98% and 11.1%) and Process B (69.58% and 17.64%). The calculated CE (85.68%) for Process C justifies for excess stoichiometry in reaction conditions and 90% yield of the product even though number of carbons remains the same. As RME includes all reactant mass, yield, and atom economy, it is the most useful metric to determine the greenness of the process. Calculations of RME gave even more noteworthy

Table 3. Green Metrics (AE, AEf, CE, RME, OE and MP) for Processes A-C

Process	Isolation steps	Yield (%)	AE (%)	AEf (%)	CE (%)	RME (%)	OE (%)	MP (%)
A	4	19.14	57.98	11.1	4.54	1.98	3.42	0.26
B	3	25.35	69.58	17.64	61.53	15.8	22.71	0.13
C	1	90	83.92	75.53	85.68	72.0	85.80	5.48

The value closer to 100%, the greener the process

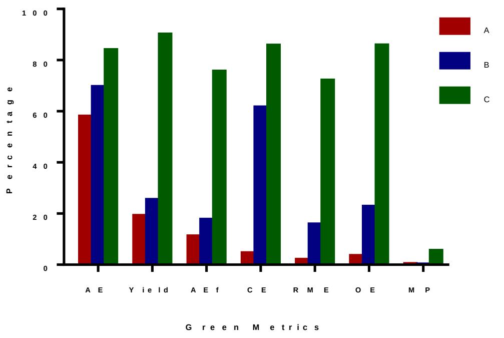
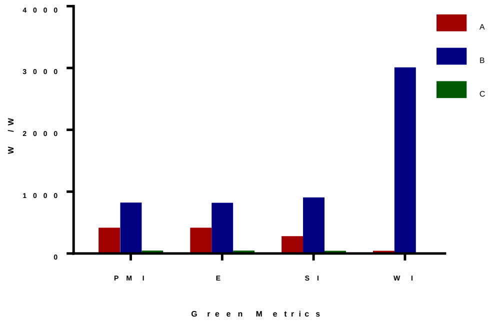


Table 4. Green Metrics (PMI, E factor, SI and WI) for Processes A-C

Process	PMI (g/g)	E (g/g)	SI (g/g)	WI (g/g)
A	389.67	388.67	250.44	14.15
B	794.31	793.31	877.81	2982.46
C	18.26	17.26	14.56	2.31

Lower is the value, better is the process



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results for Process C (72.0%) compared to Process A (1.98%) and Process B (15.8%). RME is calculated based on the purified product, the solvent used for purification takes account. Process A has four purification steps, its RME (1.98%) is worse than Process B (15.8%), and much worse than Process C (72.0%). Similarly, PMI evaluation also showed Process C (18.26) is far more superior to Process A (389.67) and Process B (794.31). Moreover, the OE of Process A (3.42%) and B (22.71%) are very less compared to Process C (85.80%). Mass productivity is useful for industry as it focusses on resource consumption. The MP for the Processes A (0.26%) and B (0.13%) are also less than that of Process C (5.48%). This means that mass being wasted in making the product is more in Processes A and B in comparison to Process C. The RME and MP of Process C also rationalize less than 100% yield and the need for a 10% molar excess of *N*-propylmaleimide.

Solvents including water used in a chemical process is also recognized as a threat to environment and therefore, reduction in their usage is the need of the hour. Thus, solvent intensity (SI) and water intensity (WI) values were determined. Large excess of solvent including water were used in processes A and B compared to process C leading to enormous difference in their values.

Conclusions

A highly efficient and metal catalyst-free synthesis of pyrroloquinolinediones and quinolinedicarboxylates is developed through a one-pot and quadruple reaction sequence involving denitrogenation/benzisoxazole formation/aza-Diels-Alder cycloaddition/dehydrative aromatization. Other than reaction solvent MeCN, no catalyst and additives were used, and only N_2 gas and H_2O were generated as byproducts from the reaction process. Compared to two reported methods for pyrroloquinolinediones, the new method is much more efficient and better in all aspects of green chemistry metrics analysis.

Acknowledgements

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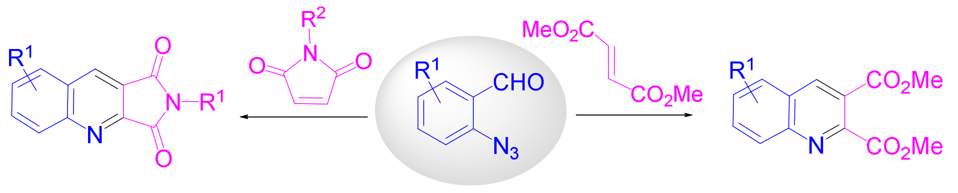

- **Catalyst-free synthesis**
- **Only N_2 and H_2O are produced as byproducts**
- **One-pot synthesis involving four reaction steps**
- **More efficient than reported methods for pyrroloquinolinediones**

Abstract: A method for catalyst-free synthesis of pyrroloquinolinediones and quinolinedicarboxylates is developed through a one-pot synthesis involving denitrogenation of azide, benzisoxazole formation, aza-Diels-Alder cycloaddition, and aromatization for pyridine. Only a stoichiometric amount of N_2 and H_2O is produced as byproducts. Green metrics analysis indicated that this method is much more efficient than two reported methods for the synthesis of pyrroloquinolinediones.