A Tandem [3+2] Cycloaddition–Elimination Cascade Reaction to Generate Pyrrolo-[3,4-*c*]pyrrole-1,3-diones

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Abstract: An efficient tandem [3+2] cycloaddition–elimination cascade sequence has been developed enabling assembly of the pharmacologically relevant pyrrolo-[3,4-*c*]pyrrole-1,3-dione chemotype. The strategy involves simple mixing of readily accessible oxazolin-2-ones and pyrrole-2,5-diones in the presence of base under mild conditions, rendering the title compounds in typically excellent yields. Of note, this route allows for installation of three points of diversity and is ideal for combinatorial applications and parallel synthesis production campaigns.

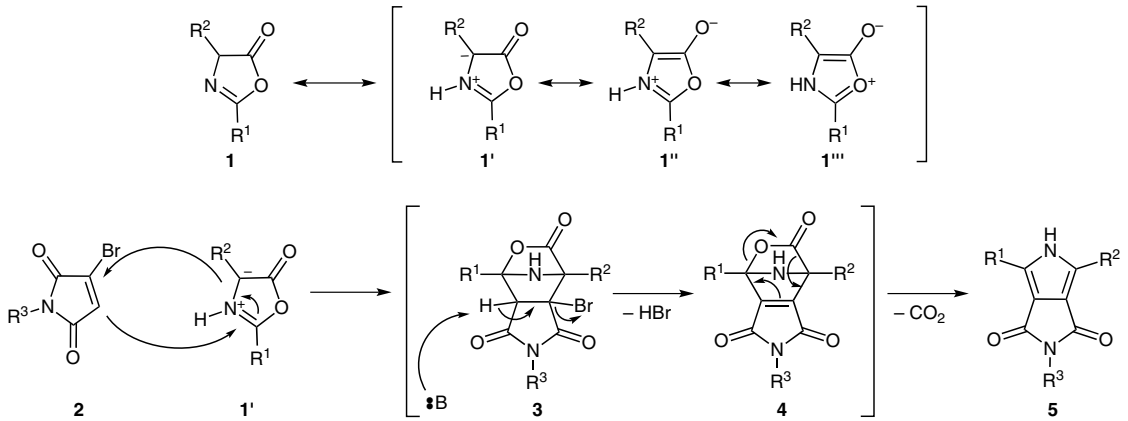
Key words: cycloaddition, elimination, tandem reaction, bicyclic compounds, ylides

The pyrrolo-[3,4-*c*]pyrrole-1,3-dione moiety is an interesting multipurpose scaffold that can be found in pharmacologically relevant molecules displaying several different activities encompassing analgesic,[2] antidepressant,[3] antineoplasic,[4] hypocholesterolemic, and hypolipidemic[5] properties. Moreover, such a nucleus is contained in macromolecules such as porphyrins[6] and porphins,[7] which have potential applications in photodynamic therapy.[8]

Notwithstanding the enticing scenario mentioned above, this chemotype has been quite underexplored to date, and only a small number of scientific works dealing with its applications in the medicinal chemistry arena are available in the literature.

In this context, scarce synthetic accessibility is a severe limitation hampering extensive studies and pharmacological screening of pyrrolo-[3,4-*c*]pyrrole-1,3-diones. General strategies for the preparation of such compounds in fact rely on lengthy multistep protocols consisting of unfriendly and time-consuming procedures, resulting in very low overall yields after multiple synthetic operations and purifications steps.

For example, methodologies using α,β-diacetylsuccinate as the starting material usually involve five steps,[9] and another approach employing 3,4-dicarboxypyrroles as key intermediates involves eight synthetic steps with overall yields below 9%.[10] Prompted by our experience[11] in designing concise, efficient, and diversity-enabling routes toward druglike heterocyclic chemotypes, and inspired by a recent publication describing the use of oxazolin-2-ones **1** as partners in 1,3-dipolar cycloadditions with dipolarophiles,[12] we envisioned the possibility to engage **1** in a cycloaddition—elimination process with pyrrole-2,5-diones **2**. Such a chemical transformation was expected to be triggered by the well-known azomethine ylide character[13] of the resonance form **1′** and to render the title compounds **5** after elimination of hydrobromic acid and carbon dioxide during the breakdown of intermediate species **3** and **4**, respectively (Scheme 1).



Scheme 1 Proposed mechanism for the route toward products **5**

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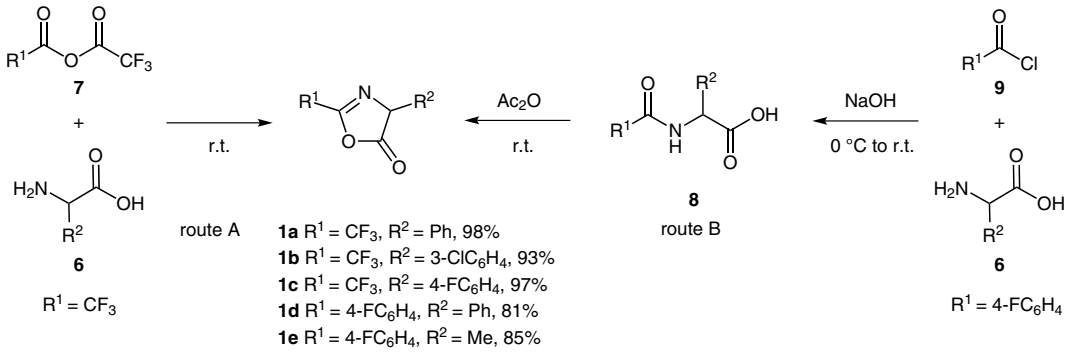
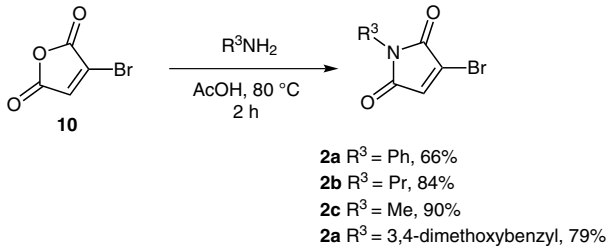


Scheme 2 Preparation of oxazolin-2-ones **1**

The main advantage of this convergent protocol over existing procedures is the ready availability of the starting materials **1** and **2**, which can be both prepared from commercially available products by means of extremely straightforward methodologies. As such, oxazolin-2-ones bearing a trifluoromethyl substituent in the 4-position were obtained in nearly quantitative yields by simply mixing (route A) α-amino acids **6** and trifluoroacetic anhydride **7**.[14,15] Alternatively (route B), building blocks **1**, endowed with a 4-fluorophenyl residue in the 4-position, could easily be accessed via a two-step procedure involving a coupling between acyl chlorides **9** and α-amino acids **6** followed by cyclodehydration (Scheme 2).[16,17] It is noteworthy that none of these synthetic operations required subsequent purifications, as the products were always recovered devoid of significant impurities.

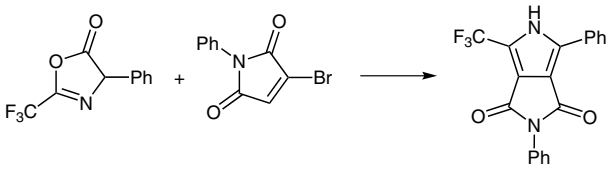
In a similarly operationally friendly fashion, a reaction between bromomaleic anhydride **10** and primary amines in acetic acid[18] smoothly afforded pyrrole-2,5-diones in high yields (Scheme 3).[19]



Scheme 3 Preparation of pyrrole-2,5-diones **2**

Having prepared in a straightforward manner a satisfactory diversity-enhancing pool of reactants, we then designed the key step of our protocol, the one-pot, sequential cycloaddition–elimination process that led to the title compounds **5** (Table 1). Since 1,3-dipolar cycloadditions are known to work best in nonpolar solvents, due to the concerted nature of their mechanism,[13d] toluene was selected as the reaction medium. For the sake of practical ease and cost reduction, reactions should ideally be carried out in the absence of catalyst or additive. In this context, [3+2] cycloadditions often proceed spontaneously. Consequently, initial studies focused on simply mixing the two starting materials **1** and **2** in toluene and stirring the resulting solution overnight. Unfortunately, stirring at room temperature (Table 1, entry 1) and prolonged heating at 80 °C (Table 1, entry 2) both proved unsuccessful, and no reaction took place. Addition of a base was therefore investigated, as it was thought likely to trigger both the formation of the azomethine ylide form **1′** and the dehydrobromination of intermediate **3**. Gratifyingly, one equivalent of 1,8-diazabicycloundec-7-ene (DBU) proved to be capable of promoting the process (Table 1, entry 3), resulting in a moderate 46% yield after 24 hours at room temperature. Increments of up to two equivalents of DBU were thus evaluated, and a dramatic improvement in yield and shortening in reaction time was observed (Table 1, entry 4). Finally, when diisopropylethylamine (DIPEA) was employed (Table 1, entry 5), clean, almost quantitative formation of **5a** was detected within 15 minutes, and the expected product was recovered in a 91% yield upon column chromatography.

Table 1 Optimization of the Cycloaddition–Elimination Protocol[20]

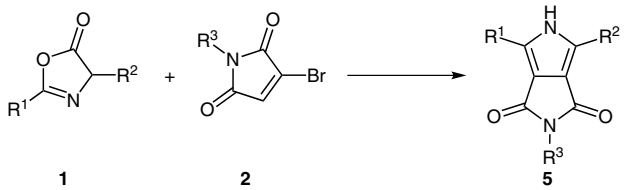


Entry	Conditions	Yield (%)
1	toluene, r.t., 24 h	n.r.[a]
2	toluene, 80 °C, 24 h	n.r.[a]
3	toluene, DBU (1 equiv), r.t., 24 h	46
4	toluene, DBU (2 equiv), r.t.,15 min	84
5	toluene, DIPEA (2 equiv), r.t., 15 min	91

[a] n.r. = no reaction.

At this stage, in addition to mass spectrometry and NMR experiments, the structure of **5a** was unambiguously determined by means of X-ray crystallography.[21]

Table 2 Scope of the Cycloaddition–Elimination One-Pot Protocol



1 **2** **5**

Compound	R^1	R^2	R^3	Yield (%)
5a	CF_3	Ph	Ph	91
5b	CF_3	Ph	Me	92
5c	CF_3	Ph	Pr	84
5d	CF_3	Ph	3,4-dimethoxybenzyl	90
5e	CF_3	3-ClC_6H_4	Me	91
5f	CF_3	Ph	Pr	84
5g	CF_3	Ph	3,4-dimethoxybenzyl	90
5h	CF_3	3-ClC_6H_4	Me	78
5i	CF_3	3-ClC_6H_4	Pr	81
5j	CF_3	3-ClC_6H_4	3,4-dimethoxybenzyl	81
5k	CF_3	4-FC_6H_4	Me	82
5l	CF_3	4-FC_6H_4	Pr	86
5m	CF_3	4-FC_6H_4	Ph	85
5n	CF_3	4-FC_6H_4	3,4-dimethoxybenzyl	82
5o	4-FC_6H_4	Ph	Me	90
5p	4-FC_6H_4	Ph	Pr	87
5q	4-FC_6H_4	Ph	Ph	85
5r	4-FC_6H_4	Ph	3,4-dimethoxybenzyl	82
5s	4-FC_6H_4	Me	Me	75

With optimized conditions for the key transformation in hand, we thus explored the scope of the cycloaddition–elimination one-pot process by evaluating several combinations of building blocks **1** and **2** in order to both explore the reactivity domain and prepare a small library of products **5** endowed with three points of diversity. To our delight, the method proved to be very general, and regardless of their substitution pattern, the title compounds were always formed in a clean manner with complete conversions after 15 minutes and could be isolated in very good (75–92%) yields upon column chromatography (Table 2).

In conclusion, we have reported herein a novel, fast, and straightforward methodology for the preparation of the otherwise scarcely accessible pyrrolo-[3,4-*c*]pyrrole-1,3-dione chemotype. Starting from readily available oxazolin-2-one and pyrrole-2,5-dione building blocks, this pathway efficiently renders target molecules **5** endowed with three diversity points in a single step through an elegant 1,3-dipolar cycloaddition–elimination one-pot process. Broad scope, high yields, and extreme operational ease make this strategy ideal for high-throughput applications and will hopefully encourage the lead generation community to exploit this tool to undertake extensive investigations into the properties of this underestimated scaffold that still possesses vast untapped pharmacological potential.

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(15) **General Procedure for the Preparation of Compounds 1 (Route A), Exemplified for Compound 1b**
3-Chlorophenylglycine (5.41 mmol, 1.0 g) was added to TFAA (3 mL) in a 25 mL round-bottomed flask. The mixture

was stirred for 2 h at r.t. and excess TFAA was removed in vacuo by means of azeotroping with toluene (5 × 10 mL) to give 1.32 g (93% yield) of a yellow solid product. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.42 (t, *J* = 1.8 Hz, 1 H), 8.37–8.34 (m, 1 H), 7.63 (ddd, *J* = 8.1, 2.1, 1.0 Hz, 1 H), 7.49 (t, *J* = 8.0 Hz, 1 H), 6.28 (q, *J* = 4.0 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.2, 159.8, 135.4, 134.0, 130.6, 130.4, 129.7, 128.9, 128.7, 127.2, 125.4, 121.6, 118.8, 92.4 (q, $J_{C–F}$ = 35.5 Hz). MS: *m*/*z* = 264 $[M + H]^+$.

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(17) **General Procedure for the Preparation of Compounds 1 (Route B), Exemplified for Compound 1d**
Phenylglycine (1.0 equiv, 6.60 mmol, 1.0 g) was added to 2.0 M NaOH (20 mL) in a 100 mL round-bottomed flask. The solution was cooled to 0 °C in an ice bath, and then 4-fluorobenzoylchloride (**9**, 1.0 equiv, 6.60 mmol, 0.78 mL) was added dropwise over 20 min. The reaction was allowed to warm to r.t. and stirred for 2 h. The solution was then made slightly acidic (pH 5–6) by dropwise addition of 2.0 M HCl and was extracted with EtOAc (5 × 75 mL). The organic phase was dried over $MgSO_4$ and concentrated in vacuo to yield **8d** as white solid (1.6 g). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.96 (s, 1 H), 9.06 (d, *J* = 7.4 Hz, 1 H), 7.99 (dd, *J* = 8.4, 6.0 Hz, 2 H), 7.50–7.46 (m, 2 H), 7.39–7.24 (m, 4 H), 5.58 (d, *J* = 7.4 Hz, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.3, 166.8, 166.6, 165.7, 163.7 (d, $J_{C–F}$ = 87.9 Hz), 137.4, 132.5 (d, $J_{C–F}$ = 12.4 Hz), 130.9 (d, $J_{C–F}$ = 10.1 Hz), 130.6, 128.8, 128.6, 128.4, 127.8, 116.0 (d, $J_{C–F}$ = 21.9 Hz), 115.5 (d, $J_{C–F}$ = 21.8 Hz), 57.4. MS: *m*/*z* = 274 $[M + H]^+$. Compound **8d** (5.86 mmol, 1.6 g) was then added to Ac_2O (3 mL) in a 25 mL round-bottomed flask. The mixture was stirred for 2 h at r.t. and excess Ac_2O was removed in vacuo via azeotroping with toluene (5 × 10 mL) to give 1.36 g of a yellow solid product (81% yield over two steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15–8.07 (m, 2 H), 7.50–7.35 (m, 5 H), 7.28–7.13 (m, 2 H), 5.51 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.0, 166.9, 163.0 (d, $J_{C–F}$ = 281.9 Hz), 133.3, 130.6 (d, $J_{C–F}$ = 9.2 Hz), 129.0, 128.8, 128.2 (d, $J_{C–F}$ = 8.6 Hz), 126.8, 121.9, 116.2 (d, $J_{C–F}$= 22.3 Hz), 115.9 (d, $J_{C–F}$ = 22.2 Hz), 68.1. MS: *m*/*z* = 256 $[M + H]^+$.

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(19) **General Procedure for the Preparation of Compounds 2, Exemplified for Compound 2c**
3-Bromomaleic anhydride (1.0 equiv, 5.65 mmol, 1.0 g) was dissolved in AcOH (20 mL). Methylamine hydrochloride (1.0 equiv, 5.65 mmol, 0.37 g) was then added, and the reaction was heated at 80 °C for 3 h. Solvent was removed in vacuo, and the crude mixture was purified by column chromatography over silica gel (EtOAc–hexane 0–30%) using an ISCO^{TM} purification system to afford 0.97 g of a white solid (90% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.89 (s,1 H), 3.08 (s,3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 165.3, 131.9, 131.3, 24.6. MS: *m*/*z* = 191 $[M + H]^+$.

(20) **General Procedure for the Preparation of Compounds 5, Exemplified for Compound 5a**
4-Phenyl-2-(trifluoromethyl)oxazol-5(4*H*)-one (**1a**, 1.0 equiv, 1,3 mmol, 0.30 g) and 3-bromo-phenyl-1*H*-pyrrole-2,5-dione (**2a**, 1.0 equiv, 1,3 mmol, 0.33 g) were dissolved in toluene (20 mL). DIPEA (2.0 equiv, 2.6 mmol, 0.45 mL) was added. The reaction mixture was stirred at r.t. for 15 min. Solvent was evaporated in vacuo, and the crude material was purified by column chromatography over silica gel (EtOAc–Hexane 0–50%) using an ISCO^{TM} purification system to afford 0.44 g of a yellow solid (91% yield). Crystals suitable for X-ray diffraction studies were obtained by recrystallization of the pure product from CH_2Cl_2 and hexane. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (m, 10 H), 8.44 (s, 1 H). ^{13}C NMR (100 MHZ, $CDCl_3$): δ = 166.4, 162.0, 134.6, 133.4, 132.8, 131.9, 130.3, 129.6, 129.2, 129.1, 128.5, 126.9, 125.9, 121.9, 119.0, 29.6 (m). MS: *m*/*z* = 357 $[M + H]^+$.

(21) Complete crystallographic information for compound **5a** can be found in: Roberts, S. A.; Martinez-Ariza, G.; Dietrich, J.; Hulme, C. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2012**, *68*, 496.

