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A rare γ -pyranopyrazole skeleton: design, one-pot synthesis and computational study†

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Drawing upon a consecutive amide coupling and intramolecular cyclisation pathway, a one-pot, straightforward synthetic route has been developed for a range of pyrazole fused γ -pyrone derivatives. The reaction mechanism proposed for the chemoselective formation of γ -pyranopyrazole is furthermore fully supported by experimental and computational studies.

Heterocyclic compounds bearing a pyrone scaffold (e.g., 4-pyrone or γ -pyrone) exhibit an array of biological and pharmacological activities.¹ Since the biological activity of the pyrone ring is closely linked to the core structure's substitution pattern, incorporating other ring motifs into the pyrone skeleton could greatly contribute to the parent molecule's biological activity.² In terms of biological diversity, constructing ring-fused pyrone derivatives has attracted significant attention; however, despite widespread interest in and efforts toward constructing new pyrone derivatives, ring-fused pyrone derivatives remain extremely rare,³ given the lack of practical and effective synthetic protocols and guidelines for their construction.

Representing an unusual example of a fused pyrone ring, the pyranopyrazole ring system can participate in diverse biological activities including analgesic, anti-inflammatory, antimicrobial, fungicidal, and cytotoxic activities.⁴ Certain derivatives of pyranopyrazoles have been evaluated for their affinity to bind with bovine brain adenosine receptors.⁵ At the same time, the γ -pyranopyrazole ring system is photoactive and apt to undergo photochemical reactions such as photo-dimerization and photocleavage.⁶

The general method for preparing the known pyrano[3,2-*c*]pyrazole skeleton relies on a two-step synthetic process, which Gelin *et al.* have described (Fig. 1).⁷ Over the years, improved versions of the method have been published,⁸ most of which however still employ harsh reaction conditions (*i.e.*, refluxing in acetic or sulphuric acid). Deng *et al.* have recently intro-

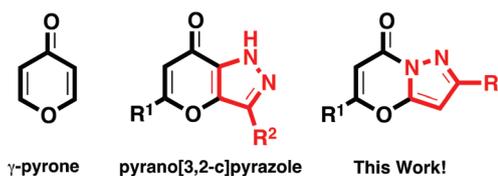


Fig. 1 Structure of γ -pyrone and γ -pyranopyrazole.

duced an elegant approach to the same γ -pyranopyrazole skeleton that relies on a tandem cyclisation process employing certain diazo compounds as starting materials.⁹ Nevertheless, other concise methods of constructing new γ -pyrone structures with potential biological activities continue to be in demand.

In response, we herein report a straightforward, one-pot synthetic protocol for constructing γ -pyranopyrazoles with a rare structural skeleton. This rare γ -pyranopyrazole skeleton differs from the common skeleton insofar as the nitrogen of the pyrazole ring is located on the bridge of the fused ring system (Fig. 1). To the best of our knowledge, only one report has described the preparation of this skeleton, namely as a low-yield by-product that remains to be thoroughly investigated.¹⁰

As part of our continued interest in synthesizing fluorescent labelling molecules, we have outlined a synthetic approach for preparing 1,5-diazabicyclo [3.3.0]octadienediones (**D**) (9,10-dioxabimanes) (Scheme 1). We proposed a two-step synthetic pathway, first involving a classical amide coupling between pyrazolone (**A**) and 2-propionic acid (**B**) (Scheme 1). Compound **C** was anticipated to cyclize in an intramolecular hydroamination process to yield the expected bimane structure (**D**). Surprisingly, however, instead of producing bimane (**D**), compound **C** cyclized unexpectedly from the oxygen atom over the alkyne to yield compound **E**: a γ -pyrone derivative fused with a pyrazole ring. We thus experimentally investigated the

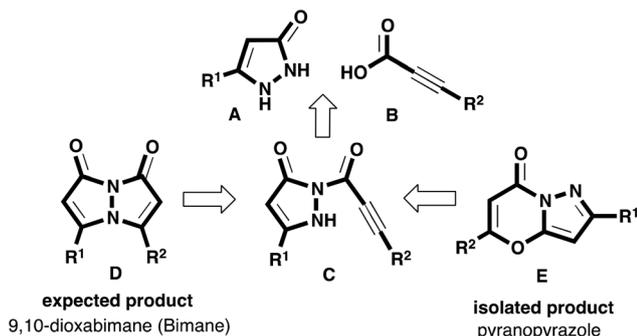
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Scheme 1 Retrosynthetic approach for the preparation of γ -pyranopyrazole.

mechanism for the chemoselective formation of γ -pyranopyrazole (**E**) over bimane (**D**), the results of which were unambiguously supported by theoretical calculations.

We commenced our investigation by optimizing the reaction conditions for C–N coupling, which uses pyrazolone (**1a**) and phenylpropionic acid (**2a**) as the model substrates (Fig. 2).

The reaction of **1a** with **2a** in the presence of classical coupling reagents such as dicyclohexylcarbodiimide (DCC) and *N,N*-dimethyl-4-aminopyridine (DMAP) was performed in various solvent systems and followed carefully by thin-layer chromatography (TLC) and nuclear magnetic resonance (NMR) spectroscopy. The efficacy of C–N bond formation greatly depended on the nature of the solvent system. The reaction of **1a** with **2a** proceeded smoothly in general, though most quickly (1 h, >95% conversion) in tetrahydrofuran (THF), whereas the conversion time of **1a** in alternative solvent systems (*e.g.* DCM and CH_3CN) was quite longer (7–16 h). When 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI, 1.2 equiv.) was used as the coupling reagent, no dramatic differences in either conversion or reaction time were observed. For practical reasons, DCC was chosen as the coupling agent in the optimization study, in which the reaction conditions for the first coupling step used a 1 : 1 ratio of both substrates (**1a** and **2a**), with a combination of DCC (1.2 equiv.) and DMAP (0.3 equiv.) in THF at room temperature.

Under these conditions, the model reaction yielded the amide **3aa** along with a trace amount of a fluorescent molecule **6aa**, as observable on the TLC plate. The chemical identity of **6aa** was initially determined by mass spectrometry analysis as the expected compound with a bimane structure (**D**), since the mass data of the compound agreed closely with the expected mass data of bimane [MS (EI, m/z): 282.2 (M^+)]. However, after

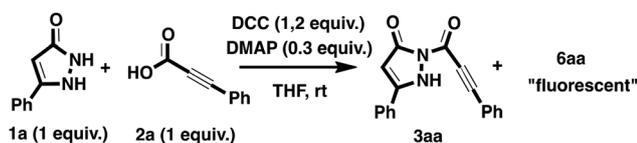


Fig. 2 Optimized reaction conditions for the amide formation step.

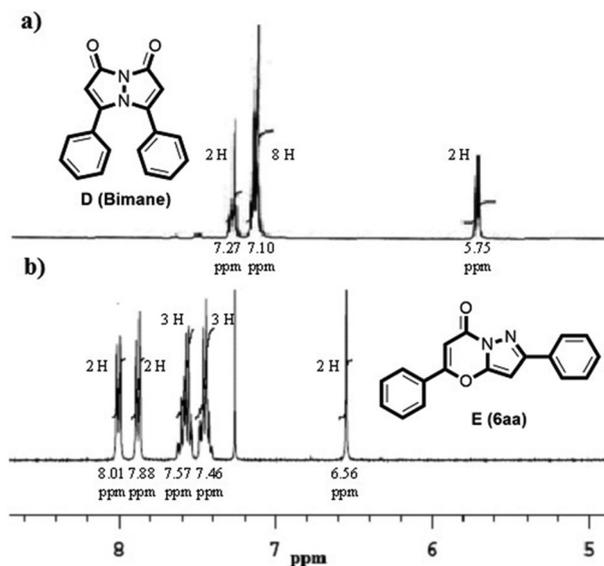


Fig. 3 Comparative $^1\text{H-NMR}$ spectra of (a) bimane (**D**) and (b) compound **E** (**6aa**).

a close inspection of its $^1\text{H-NMR}$ spectrum, we discovered that the phenyl ring protons of the unknown structure resonated at distinctly different frequencies, which contradicted the $^1\text{H-NMR}$ data of the reference bimane derivative shown in the literature.¹⁰ In fact, the phenyl ring protons of a symmetric bimane structure were expected to resonate at almost the same frequencies, a surprising observation that casts doubt on an alternative molecular structure (Fig. 3).

To further inspect the structure of the unknown product, we performed X-ray diffraction analysis on the single crystal of **6aa** recrystallized over a cold hexane–DCM solvent system. Fortunately, the fluorescent molecule, first assigned as a bimane structure (**D**), was in fact a γ -pyranopyrazole derivative (**6aa**) bearing the chemical structure displayed in Fig. 4.

Having unambiguously clarified the chemical identity of the fluorescent compound as a pyrazole-fused γ -pyrone derivative and having optimized the conditions of the first reaction, we next focused our attention on intramolecular cyclisation.

To this end, the amide **3aa** prepared *in situ* was treated respectively with a series of bases, including Cs_2CO_3 , K_2CO_3 , DBU, and Et_3N (1 equiv. of each), and added to the reaction

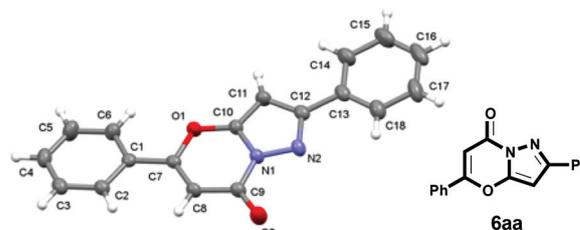


Fig. 4 X-ray diffraction analysis of compound **6aa** with thermal ellipsoids drawn at the 40% probability level.

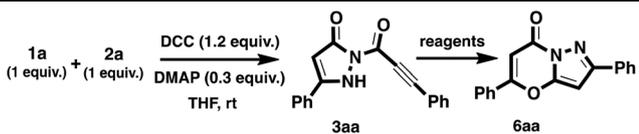


vessel soon after the starting materials were entirely consumed, as revealed on the TLC plate (*ca.* 0.5–1.0 hours). Only in the presence of Cs₂CO₃ (1 equiv.) in the one-pot protocol, the cyclisation step proceeded smoothly and produced **6aa** in a good yield (82%); (Table 1, entry 3). Consistent with other reports,^{11a-c} Cs₂CO₃ showed superior activity compared to other bases due to its mild base strength. Increasing the equivalency of Cs₂CO₃ showed no observable contribution to improving the yields (Table 1, entry 6), whereas lowering the amount of the base to catalytic levels (0.1 equiv.) negatively affected both the reaction yield and time (Table 1, entry 5). Importantly, in the presence of acidic reagents such as CF₃COOH (Table 1, entry 11) no cyclisation was monitored, while at elevated temperatures the cyclisation could be triggered to some extent (Table 1, entry 12).

Transition metal-catalysed alkyne activation reactions have been common in synthetic chemistry and have attracted great attention during the last decade. With this in mind, we aimed to substitute the base with a Lewis acidic metal species in the hope of catalysing the intramolecular cyclisation step more efficiently than with any other base. Surprisingly, none of the tested alkynophilic metal species had enough power to catalyse intramolecular cyclisation. Namely, in the presence of alkynophilic metal species such as AuCl₃, CuI, AgSbF₆ and Pd(OAc)₂, no cyclisation occurred, likely due to the deactivation of the metal species by either the DMAP or DCC reagents present in the one-pot environment (Table 2, entries 6–9). In fact, employing a base¹¹ instead of a metal species for a chemical process is advantageous for mitigating environmental problems such as metal pollution and metal toxicity.

Given these results, we eventually established that the most suitable coupling partners for the one-pot synthetic protocol

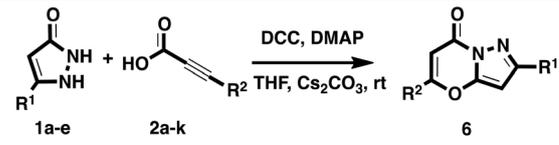
Table 1 Effect of certain bases and metal ion additives on the cyclisation of **3aa**



Entry	Reagents ^a	Time ^c (h)	Yield ^b 6aa (%)
1	Et ₃ N	3	34
2	K ₂ CO ₃	4	60
3	Cs ₂ CO ₃	3	82
4	DBU	3	38
5	Cs ₂ CO ₃ (0.1 equiv.)	8	40
6	Cs ₂ CO ₃ (2 equiv.)	3	85
7	AuCl ₃ (0.1 equiv.)	24	<1 (trace)
8	AgSbF ₆ (0.1 equiv.)	24	Trace
9	CuI (0.1 equiv.)	24	Trace
10	Pd(OAc) ₂ (0.1 equiv.)	24	Trace
11	CF ₃ COOH (3 equiv.)	8	Trace
12	None ^d	6	25
13	DMAP ^e	4	35

^a 1 equivalent of the reagents, otherwise indicated. ^b Isolated yields. ^c Reaction time at room temperature. ^d Without any additional reagent at 80 °C. ^e 3 equiv. of DMAP.

Table 2 Substrate scope for the one-pot process



Entry	1 (R ¹)	2 ^a (R ²)	6	Time ^c (h)	Yield ^b (%)
1	1a (Ph)	2a (Ph)	6aa	3	82
2	1a	2b (H)	6ab	3	25
3	1a	2c (Me)	6ac	3	57
4	1a	2d (<i>n</i> -Pent)	6ad	3	50
5	1a	2e (4-MeC ₆ H ₄)	6ae	3	80
6	1a	2f (4-MeOC ₆ H ₄)	6af	3	85
7	1a	2g (4-ClC ₆ H ₄)	6ag	3	74
8	1a	2h (2-MeC ₆ H ₄)	6ah	4	73
9	1a	2i (3-MeC ₆ H ₄)	6ai	4	75
10	1a	2j (3,5-(CF ₃) ₂ C ₆ H ₃)	6aj	5	73
11	1b (Me)	2a (Ph)	6ba	5	47
12	1b	2e (4-MeC ₆ H ₄)	6be	6	50
13	1b	2j (3,5-(CF ₃) ₂ C ₆ H ₃)	6bj	6	45
14	1c (<i>p</i> -tolyl)	2a	6ca	4	85
15	1d (<i>p</i> -Cl-Ph)	2a	6da	4	90
16	1e (<i>m</i> -tolyl)	2a	6ea	4	76
17	1a	2k (4-MeOCOC ₆ H ₄)	6ak	4	81

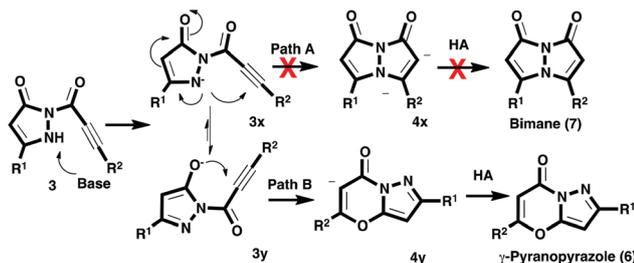
^a 1 equivalent of the reagents, otherwise indicated. ^b Isolated yields. ^c Reaction time at room temperature.

were DCC and DMAP, the solvent was THF, and the reagent driving cyclisation to completion was Cs₂CO₃ (Table 1, entry 2). The reaction time for the one-pot reaction at room temperature varied from 3 to 6 h, depending on the structure of the substrates used (Table 2).

With the optimized conditions in hand, we next explored the scope and limitations of the sequential amide formation and cyclisation process by testing the reactions of various propiolic acid derivatives (**2a–k**) with a range of pyrazolone derivatives (**1a–e**) (Table 2). The substrate scope is shown in Table 2. A variety of aryl propiolic acid derivatives bearing electron-donating or -withdrawing groups as substituents on the 2-, 3-, and 4-positions of the aryl ring underwent reactions smoothly and yielded the desired compound in moderate to good yields. Electronic properties of the substituents displayed a slight effect on both the yield and reaction time; namely, yields for substrates bearing electron-donating groups on the aryl ring were slightly higher. Although the cyclisation of aliphatic propiolic acid derivatives (**2b–d**) proceeded as well, the rate of cyclisation and the reaction yields were distinctly lower than that of aryl propiolic acid derivatives (**2a, 2e–k**).

Based on the experimental and computational results, we proposed a reasonable mechanism for the formation of γ -pyranopyrazole as outlined in Scheme 2. Mechanistically, the reaction proceeds by way of a two-step consecutive process, the first step of which is a classical C–N coupling. Compound **3**, formed in the first step, subsequently undergoes a base-mediated intramolecular 6-*endo-dig* ring closure from the oxygen atom over the alkyne to yield γ -pyranopyrazole (**6**) (Scheme 2).





Scheme 2 Proposed reaction mechanism supported by theoretical calculations.

Selective formation of the γ -pyranopyrazole ring over the bimane ring was computationally investigated to explain the product selectivity (Scheme 2). Geometrical parameters were optimized with the density-functional theory (B3LYP/6-311G++(d,p)).^{12–14} Reaction energies and activation energy barriers are shown in Table S2 (see the ESI[†]), and the potential energy profile of the cyclisation step is shown in Fig. 5.

The TS (transition state) of 3x/4x and 3y/4y are considered to be the rate-determining steps for structures 7 and 6, respectively. Calculations confirmed that the activation energy barrier for forming intermediate 4x was considerably higher than 4y (Table S2, entries 10 and 14 and see the ESI[†]); namely, the difference between the reaction barriers of 4x and 4y was calculated to be 7.1 kcal mol⁻¹ (Fig. 5). Furthermore, the TS theory rate constants at room temperature were calculated to be 5.0×10^{-4} s⁻¹ and 47 s⁻¹ for 4x and 4y, respectively (Table S2, see the ESI[†]). Accordingly, compound 6 is the kinetically favourable product, which also reveals that compound 7 was unobservable.

The electrostatic potential map (EPM) of 3cb (R¹ and R² = H) was calculated to investigate the resonance hybrid structures that significantly contributed to the structure of compound 3. We surmised that the resonance structure with the negatively charged oxygen atom was the dominant hybrid of 3cb. To verify this assumption, we considered the structure of 3cb (Fig. S1, see the

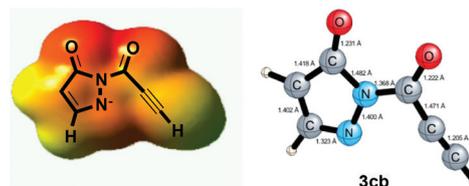


Fig. 6 Electron density potential map of structure 3cb.

ESI[†]), which shows that the C–O bond length (1.231 Å) in the pyrazolidine fragment is noticeably longer than that of the regular C–O double bond (1.222 Å). As such, the C–O bond of the pyrazolidine fragment has a single-bond character, which accounts for the intermolecular cyclisation over the oxygen atom. Also, the EPM of 3cb (Fig. 6) demonstrates that the negative charge is located on the oxygen atom of the pyrazolidine ring. In short, a favourable geometry associated with the formation of γ -pyrone (6) never allowed compound 3 to undergo a 5-*exo-dig* hydroamination ring closure necessary to yield a bimane ring (7).

Most of the γ -pyrone derivatives synthesized herein displayed strong fluorescence emission under ultraviolet light. For this reason, we further determined the photophysical properties of all new γ -pyrone derivatives by measuring their absorption and emission wavelengths, fluorescence quantum yields, and absorption coefficients. Table S1[†] summarizes all these properties for all new γ -pyrone derivatives. Among them, compounds 6aa, 6ad and 6ag displayed exceptional photophysical features presenting great potential for use in applications for biochemical labelling and light-emitting devices.

Conclusions

In summary, we developed a one-pot, two-step synthetic method for constructing a range of highly emissive γ -pyranopyrazole derivatives. Remarkably, this one-pot system is based on a transition metal-free synthetic protocol involving the use of an inorganic base (e.g. Cs₂CO₃) to promote an intramolecular 6-*endo-dig* cyclisation process. Based on computational studies, we ultimately proposed a reasonable mechanism for product selectivity.

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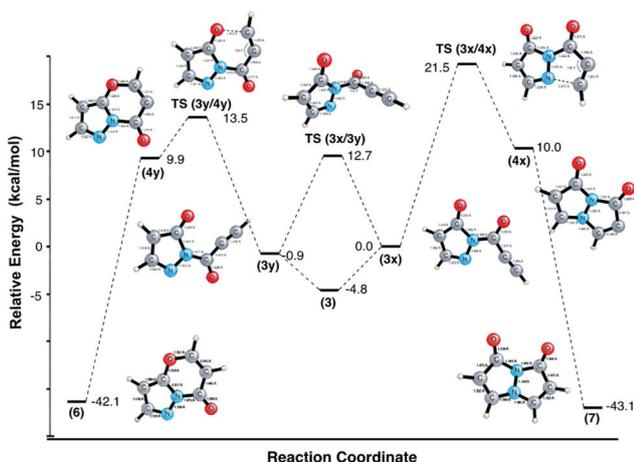


Fig. 5 Potential energy profile related to the formation of the products, intermediates and transition states. Energies of structures 3, 6, and 7 are computed relative to 3x + H, since they have different stoichiometry.



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