Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2016, **14**, 7490

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

Muhammed Üçüncü,[a] Ceren Cantürk,[a] Erman Karakuş,[a] Hüseyin Zeybek,[a] Uğur Bozkaya,[b] Emine Soydaş,[c] Ertan Şahin[c] and Mustafa Emrullahoğlu*[a]

Received 19th May 2016,
Accepted 5th July 2016

DOI: 10.1039/c6ob01099g

www.rsc.org/obc

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 photodimerization 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 introduced 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.

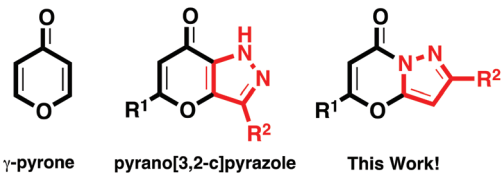


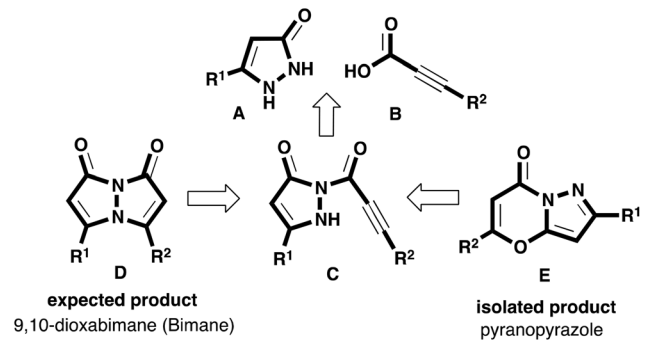
Fig. 1 Structure of γ-pyrone and γ-pyranopyrazole.

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-propiolic 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

[a]*Department of Chemistry, Faculty of Science, İzmir Institute of Technology, Urla, 35430 Izmir, Turkey. E-mail: mustafaemrullahoglu@iyte.edu.tr*
[b]*Department of Chemistry, Hacettepe University, Ankara 06800, Turkey*
[c]*Department of Chemistry, Atatürk University, Erzurum 25240, Turkey*

†Electronic supplementary information (ESI) available: Experimental procedures, characterization of new compounds, spectral data, computational results and crystallographic data. CCDC 1456335. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6ob01099g



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 phenylpropiolic 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

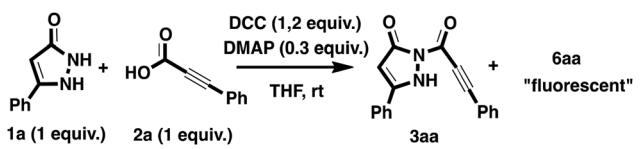


Fig. 2 Optimized reaction conditions for the amide formation step.

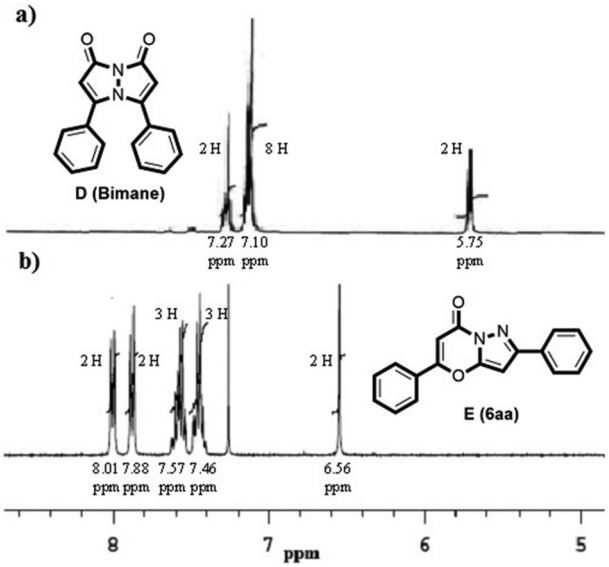


Fig. 3 Comparative ^{1}H-NMR spectra of (a) bimane (**D**) and (b) compound **E** (**6aa**).

a close inspection of its ^{1}H-NMR spectrum, we discovered that the phenyl ring protons of the unknown structure resonated at distinctly different frequencies, which contradicted the ^{1}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

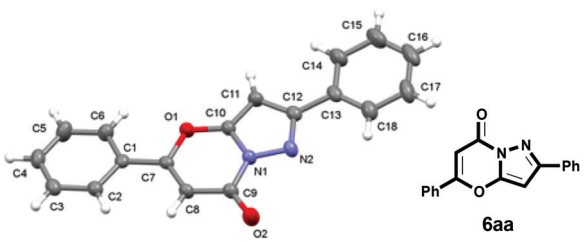


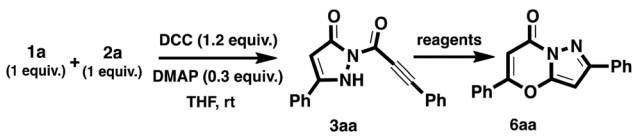
Fig. 4 X-ray diffraction analysis of compound **6aa** with thermal ellipsoids drawn at the 40% probability level.

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 Cs_2CO_3 (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] Cs_2CO_3 showed superior activity compared to other bases due to its mild base strength. Increasing the equivalency of Cs_2CO_3 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 CF_3COOH (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 $AuCl_3$, CuI, $AgSbF_6$ 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 base[11] 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 were DCC and DMAP, the solvent was THF, and the reagent driving cyclisation to completion was Cs_2CO_3 (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).

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

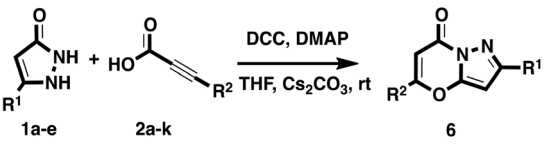


3aa 6aa

Entry	Reagents[a]	Time[c] (h)	Yield[b] **6aa** (%)
1	Et_3N	3	34
2	K_2CO_3	4	60
3	Cs_2CO_3	3	82
4	DBU	3	38
5	Cs_2CO_3 (0.1 equiv.)	8	40
6	Cs_2CO_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_3COOH (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



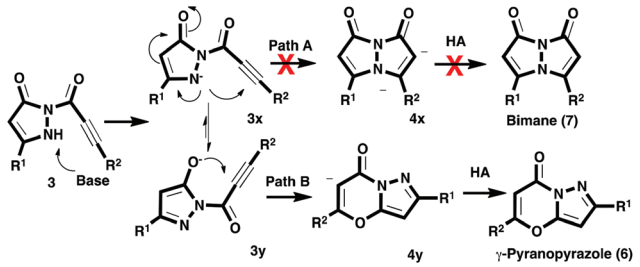
1a-e 2a-k 6

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** (*n*-Pent)	**6ad**	3	50
5	**1a**	**2e** (4-MeC_6H_4)	**6ae**	3	80
6	**1a**	**2f** (4-$MeOC_6H_4$)	**6af**	3	85
7	**1a**	**2g** (4-ClC_6H_4)	**6ag**	3	74
8	**1a**	**2h** (2-MeC_6H_4)	**6ah**	4	73
9	**1a**	**2i** (3-MeC_6H_4)	**6ai**	4	75
10	**1a**	**2j** (3,5-$(CF_3)_2C_6H_3$)	**6aj**	5	73
11	**1b** (Me)	**2a** (Ph)	**6ba**	5	47
12	**1b**	**2e** (4-MeC_6H_4)	**6be**	6	50
13	**1b**	**2j** (3,5-$(CF_3)_2C_6H_3$)	**6bj**	6	45
14	**1c** (*p*-tolyl)	**2a**	**6ca**	4	85
15	**1d** (*p*-Cl-Ph)	**2a**	**6da**	4	90
16	**1e** (*m*-tolyl)	**2a**	**6ea**	4	76
17	**1a**	**2k** (4-$MeOCOC_6H_4$)	**6ak**	4	81

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

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** (R^1 and R^2 = 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 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**).

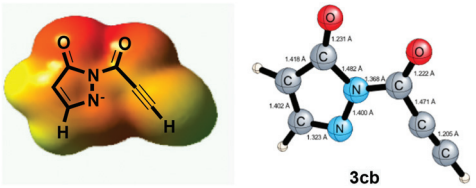


Fig. 6 Electron density potential map of structure **3cb**.

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.

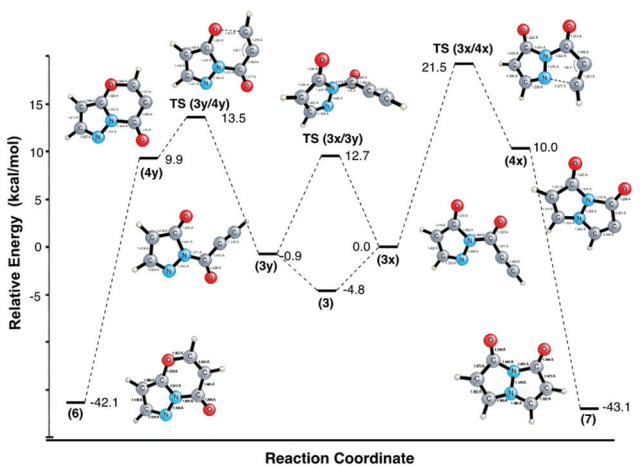


Fig. 5 Potential energy profile related to the formation of the products, intermediates and transition states. Energies of structures **3**, **6**, and **7** are computed relative to **3x** + H, since they have different stoichiometry.

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.* Cs_2CO_3) to promote an intramolecular 6-*endo*-*dig* cyclisation process. Based on computational studies, we ultimately proposed a reasonable mechanism for product selectivity.

Acknowledgements

We thank the İzmir Institute of Technology (IZTECH) and TUBİTAK (113Z157) for financial support. U. B. acknowledges the support from the Turkish Academy of Sciences, Outstanding Young Scientist Award (TÜBA-GEBİP 2015).

Notes and references

1 (*a*) I. Abe, S. Oguro, Y. Utsumi, Y. Sano and H. Noguchi, *J. Am. Chem. Soc.*, 2005, **127**, 12709; (*b*) M. P. Sibi and J. Zimmerman, *J. Am. Chem. Soc.*, 2006, **128**, 13346.

2 (*a*) D. T. Puerta, J. Mongan, B. L. Tran, J. A. McCammon and S. M. Cohen, *J. Am. Chem. Soc.*, 2005, **127**, 14148; (*b*) M. M. M. Pinto, M. E. Sousa and M. S. Nascimento, *J. Curr. Med. Chem.*, 2005, **12**, 2517; (*c*) K. Morisaki and S. Ozaki, *Chem. Pharm. Bull.*, 1996, **44**, 1647; (*d*) D. Garey, M. L. Ramirez, S. Gonzales, A. Wertsching, S. Tith, K. Keefe and M. R. Pena, *J. Org. Chem.*, 1996, **61**, 4853.

3 (*a*) A. Venkatesham, R. S. Rao, K. Nagaiah, J. S. Yadav, G. RoopaJones, S. J. Basha, B. Sridhard and A. Addlagatta, *MedChemCommun*, 2012, **3**, 652; (*b*) D. R. Gorja, V. R. Batchu, A. Ettam and M. Pal, *Beilstein J. Org. Chem.*, 2009, **5**, 64; (*c*) R. Kaur, N. Taheam, A. K. Sharma and R. Kharb, *Res. J. Pharm., Biol. Chem. Sci.*, 2013, **4**, 79; (*d*) S. Lu, J. Tian, W. Sun, J. Meng, X. Wang, X. Fu, A. Wang, D. Lai, Y. Liu and L. Zhou, *Molecules*, 2014, **19**, 7169.

4 (*a*) S.-C. Kuo and L.-J. Huang, *J. Med. Chem.*, 1984, **27**, 539; (*b*) M. E. A. Zaki, H. A. Saliman, O. A. Hiekal and A. E. Z. Rashad, *Z. Naturforsch., C: J. Biosci.*, 2006, **61**, 1; (*c*) M. Parshad, V. Verma and D. Kumar, *Monatsh. Chem.*, 2014, **145**, 1857; (*d*) F. M. Abdelrazek, P. Metzl, O. Kataeval, A. Jager and S. F. El-Mahrouky, *Arch. Pharm. Chem. Life Sci.*, 2007, **340**, 543; (*e*) M. M. M. Ramiz, I. S. Abdel Hafiz, M. A. M. Abdel Reheim and H. M. Gaber, *J. Chin. Chem. Soc.*, 2012, **59**, 72; (*f*) S. R. Mandha, S. Siliveri, M. Alla, V. R. Bommena, M. R. Bommineni and S. Balasubramanian, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 5272.

5 V. Colotta, D. Catarzi, L. Cecchi and C. Martini, *Farmaco*, 1998, **53**, 189.

6 (*a*) P. Yates and M. J. Jorgenson, *J. Am. Chem. Soc.*, 1963, **85**, 2956; (*b*) N. Ishibi, M. Odani and M. Sunami, *J. Am. Chem. Soc.*, 1973, **95**, 463; (*c*) J. W. Pavlik and J. Kwong, *J. Am. Chem. Soc.*, 1973, **95**, 7914; (*d*) J. A. Barltrop, A. C. Day and C. J. Samuel, *J. Chem. Soc., Chem. Commun.*, 1977, 598; (*e*) J. A. Barltrop, A. C. Day and C. J. Samuel, *J. Am. Chem. Soc.*, 1979, **101**, 7521.

7 S. Gelin, B. Changtegrel and A. I. Nadi, *J. Org. Chem.*, 1983, **48**, 4078.

8 (*a*) J. W. Pavlik, V. Ervithayasuporn and S. Tantayanon, *J. Heterocycl. Chem.*, 2011, **48**, 710; (*b*) W. Becker, G. A. Eller and W. A. Holzer, *Synthesis*, 2005, 2583; (*c*) A. Kumar, P. Lohan, D. K. Aneja, G. K. Gupta, D. Kaushik and O. Prakash, *Eur. J. Med. Chem.*, 2012, **50**, 61; (*d*) J. W. Pavlik, V. Ervithayasuporn, J. C. MacDonald and S. Tantayanon, *ARKIVOC*, 2009, **8**, 57; (*e*) H. Kurod and H. Izawa, *Bull. Chem. Soc. Jpn.*, 2007, **80**, 780.

9 G. Deng, F. Wang, S. Lu and B. Cheng, *Org. Lett.*, 2015, **17**, 4651.

10 Z. Zheng, Z. Yu, N. Luo and X. Han, *J. Org. Chem.*, 2006, **71**, 9695.

11 (*a*) T. N. Poudel and Y. R. Lee, *Org. Biomol. Chem.*, 2014, **12**, 919; (*b*) T. N. Poudel and Y. R. Lee, *Org. Lett.*, 2015, **17**, 2050; (*c*) T. N. Poudel and Y. R. Lee, *Chem. Sci.*, 2015, **6**, 7028; (*d*) H. Vander Mierde, P. Van Der Voort and F. Verpoort, *Tetrahedron Lett.*, 2008, **48**, 6893; (*e*) X. F. Wu, S. Oschatz, A. Block, A. Spannenberg and P. Langer, *Org. Biomol. Chem.*, 2014, **12**, 1865; (*f*) S. Basceken, S. Kaya and M. Balci, *J. Org. Chem.*, 2015, **80**, 12552.

12 (*a*) A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648; (*b*) C. Lee, W. Yang and R. G. Parr, *Phys. Rev. B: Condens. Matter*, 1988, **37**, 785.

13 (*a*) K. Ishida, K. Morokuma and A. Komornicki, *J. Chem. Phys.*, 1977, **66**, 2153; (*b*) K. Fukui, *Acc. Chem. Res.*, 1981, **14**, 363; (*c*) H. P. Hratchian and H. B. Schlegel, *J. Chem. Phys.*, 2004, **120**, 9918.

14 (*a*) P. C. Hariharan and J. A. Pople, *Theor. Chem. Acc.*, 1973, **28**, 213; (*b*) A. D. McLean and G. S. Chandler, *J. Chem. Phys.*, 1980, **72**, 5639.

