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Cyclocondensation reactions of an electron deactivated 2-aminophenyl tethered imidazole with mono/1,2-biselectrophiles: synthesis and DFT studies on the rationalisation of imidazo[1,2-*a*]quinoxaline *versus* benzo[*f*]imidazo[1,5-*a*][1,3,5]triazepine selectivity switches†

Gaurav Joshi,[a] Monika Chauhan,[a] Rakesh Kumar,[a] Ankush Thakur,[a] Sachin Sharma,[a] Rajveer Singh,[b] Aabid Abdullah Wani,[c] Ashoke Sharon,[d] Prasad V. Bharatam[c] and Raj Kumar *[a,b]

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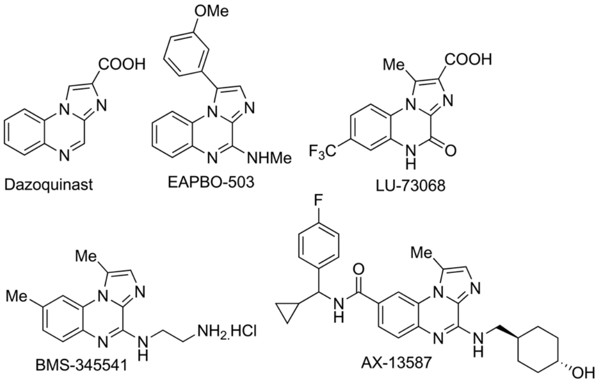
Microwave-promoted ring-closure reactions of 5-amino-1-(2-aminophenyl)-1*H*-imidazole-4-carbonitrile (**7**) with various mono/1,2-biselectrophiles are presented. The reaction of **7** with aldehydes, ketones and isocyanates produced the corresponding Pictet–Spengler (PS) products *i.e.* the imidazo[1,2-*a*]quinoxaline ring system *via* 6-*endo*-trig cyclisation. On the other hand, the reaction of **7** with $CH(OEt)_3$, and CDI resulted in the formation of benzo[*f*]imidazo[1,5-*a*][1,3,5]triazepine scaffolds *via* a 7-*exo*-trig cyclisation process. The mechanistic aspects of these ring cyclisation processes have been analysed and studied to rationalise 6- *versus* 7-membered ring formation using density functional theory (DFT). DFT calculations revealed the involvement of N-Heterocyclic Carbene (NHC) in the PS reaction mechanism.

Introduction

Nitrogen heterocycles are considered as the privileged chemotypes in pharmaceuticals as they constitute about 59% of the total US FDA approved small molecules.[1,2] Among them, imidazoquinoxaline[3,4] and imidazodiazepine[5] skeletons are widely used in practice due to their broad applications in drug discovery. In particular, imidazo[1,2-*a*]quinoxaline derivatives possess anticancer (antitubulin; EAPBo503),[6] antiallergic (dazoquinast),[3] anticonvulsant (LU-73068),[7] and kinase inhibitory[8] (BMS-345541[9] and AX-13587) activities (Scheme 1).

The available synthetic approaches for imidazo[1,2-*a*]quinoxaline(**1**)[3] either involve cyclo-condensation (ring closure) reactions of quinoxaline (path a–e) or imidazole (path f) with an appropriate electrophile (Scheme 2). Path ‘a’ involves the ring opening of aziridine of **2** upon addition of NaI and refluxing in Me_2CO.[10] Path ‘b’ deals with the intramolecular ring closure of **3** in $(CF_3CO)_2O$ and TFA.[4,11] **4** could be converted into **1** under the influence of a Pd–Cu catalyst (path ‘c’),[12] whereas path ‘d’[13] and ‘e’[14,15] involve the reaction of **5** with ethyl bromopyruvate and, with aldehyde and isocyanate, respectively. 2-Formylimidazole when treated with 2-iodoani-



Scheme 1 Imidazo[1,2-*a*]quinoxalines as potential therapeutic agents.

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[a] Department of Pharmaceutical Sciences and Natural Products, Central University of Punjab, Bathinda-151001, Punjab, India. E-mail: raj.khunger@gmail.com, rajcps@cup.ac.in
[b] Department of Pharmaceutical Chemistry, I.S.F. College of Pharmacy, Moga, 142001, India
[c] Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research (NIPER), S.A.S. Nagar, India
[d] Department of Chemistry, Birla Institute of Technology, Mesra, Ranchi, Jharkhand, 835215, India

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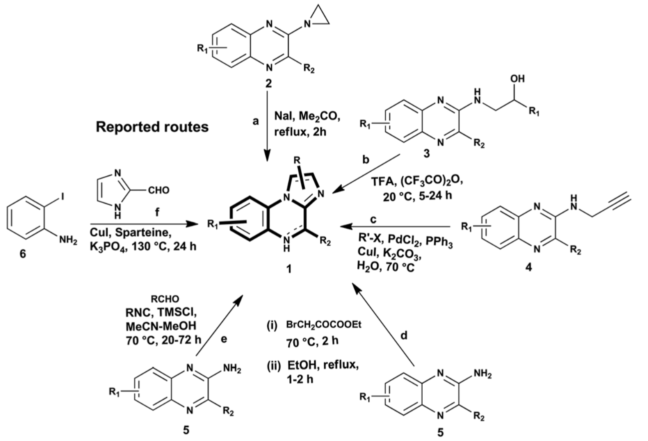
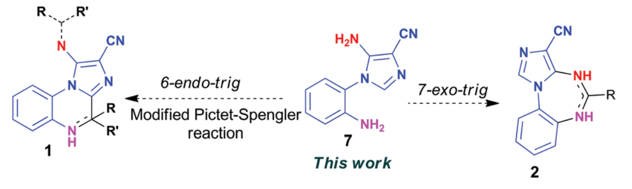


Scheme 2 Reported synthetic approaches for imidazo[1,2-*a*]quinoxaline derivatives.

line (**6**) in the presence of a Cu catalyst and additive yielded **1** (path 'f').[16] All the pathways (except path f) utilize the preassembled quinoxaline nucleus and thus limit the scope for further functionalization and synthesis of derivatives required for Structure Activity Relationship (SAR) studies in medicinal chemistry. In addition to this, the use of strong acids, heavy metals and or long reaction times warrant the need for a better method.

This prompted us to design an innovative pathway able to build imidazo[1,2-*a*]quinoxaline[17] derivatives based on a modified Pictet–Spengler (PS) reaction, which is well known for the construction of tetrahydro-β-carbolines and isoquinolines.[18] To date electron rich or deactivated rings such as pyrrole[19]/indolizine[20]/indole,[19] pyrimidine[21] and imidazole[22–25] tethered with *o*-aminophenyl are reported which undergo the PS reaction. Interestingly, the literature also contains no such reports on regioselective synthesis of imidazo[1,2-*a*]quinoxaline derivatives *via* a modified PS reaction at the C-2 position of an electron deactivated imidazole **7** (Scheme 3).

Herein, we report the microwave-assisted formation of 6-membered, imidazo[1,2-*a*]quinoxalines (**1**) *via* PS reaction and 7-endocyclised (benzo[*f*]imidazo[1,5-*a*][1,3,5]triazepines; **2**) products (Scheme 3) by the cyclocondensation of **7** with mono/bis carbon electrophiles under *p*-TsOH·H_2O (cat.) and mechanistic insights to rationalise their formation based on Density Functional Theory (DFT) calculations.

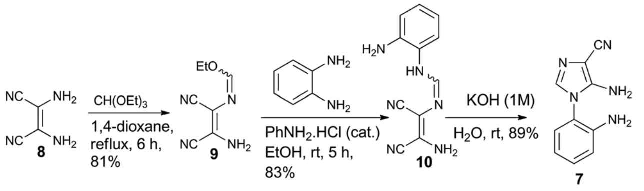


Scheme 3 Envisioned routes of formation of 6 *vs.* 7-membered cyclised products.

Results and discussion

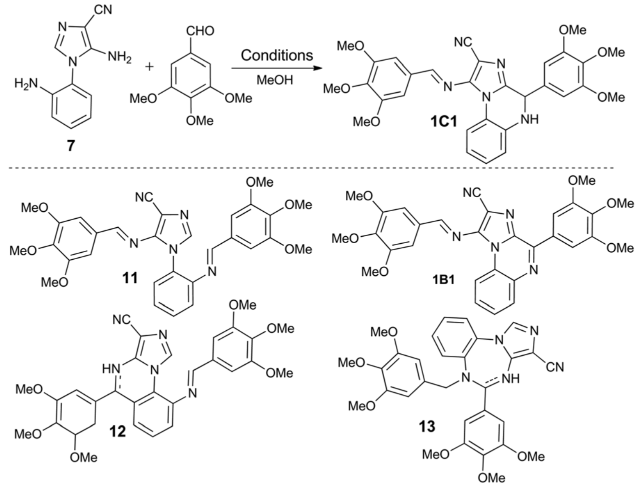
Briefly, substrate **7** was synthesized *via* condensation of diaminomaleonitrile (**8**) with $CH(OEt)_3$ in 1,4-dioxane to afford imidate ester **9**[26] which underwent substitution reaction (**10**) with *o*-phenylenediamine followed by ring formation under basic conditions (Scheme 4).

With compound **7** in hand, we then attempted to achieve the PS reaction for the construction of **1**. In order to find out the optimum reaction conditions for the PS reaction for the synthesis of designed compounds **1**, a model study was initiated; substrate **7** (1 mmol, 1 equiv.) and 3,4,5-trimethoxy benzaldehyde (2 equiv.) at rt in CH_3OH (1 mL) were condensed (Table 1). Only 10% of **11** was formed at rt after 12 h and



Scheme 4 Synthesis of substrate **7**.

Table 1 Optimization of the reaction conditions[a]



Entry	Conditions	Isolated yield[b] (%) 11	1C1	1B1
1	rt/12 h	10	—[c]	—
2	rt/*p*-TsOH·H_2O/1 h	94	—	—
3	Reflux/*p*-TsOH·H_2O/12 h	35	55	—
4	MW[e]/80 °C/1 h	98	Trace	—
5	MW[e]/80 °C/*p*-TsOH·H_2O/25 min	—	92	Trace[d]
6	MW[f]/80 °C/*p*-TsOH·H_2O/30 min	—	—	93

[a] Substrate **7** (1 mmol, 1 equiv.) and aldehyde, (2 equiv.) were mixed in MeOH (1 mL). [b] Isolated yield. [c] 5% of the product was formed under reflux after 12 h. [d] 3% of the product was formed after 1 h. [e] Reaction was carried out at 200 W in a sealed tube (Method A). [f] Reaction was carried out at 200 W in an open condenser (Method B).

heating the reaction mixture increased the yield of **11** (Table 1; entry 1). This necessitated the use of an acid catalyst; we preferred to employ *p*-TsOH·H_2O (1 mol%) which has been commonly used in the PS reaction.[21,23,27] Although the addition of the catalyst facilitated imine formation **11** (94%) at rt (entry 2), only 55% of **1C1** was obtained; the 6-*endo-trig* PS product was obtained after refluxing the reaction mixture for 12 h (entry 3). This could be due to lesser electron density at the C2-position of imidazole because of the CN group. Keeping in view the applications of microwaves (MW)[28–31] in accelerating the reaction rate and increasing the yield, the reaction was set up under MW irradiation (sealed tube) in the absence (entry 4) and presence (entry 5) of *p*-TsOH·H_2O (1 mol%). The maximum yield of **IC1** was obtained in 25 min (entry 5; method A). Exclusive product **1B1** (entry 6) was obtained while carrying out the reaction under MW for 30 min under open reflux (method B). We neither obtained **12** nor **13**.

To shed more light on regioselective PS product formation, a control experiment was set up in which C2-*H* (δ 7.16 s) of **5** was replaced with bromo by reacting **7** with NBS at rt for 1 h in MeCN[32] yielding **14** (Scheme 5). **14** (1 equiv.) when reacted with 2,3-dimethoxy benzaldehyde (2 equiv.) using method B failed to yield a ring cyclised product *via* **15** which confirmed that the PS reaction takes place at the C2-position of imidazole only.

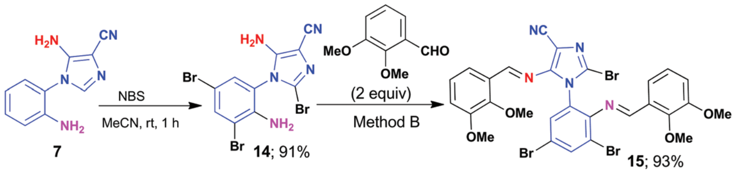
To explore the scope and limitations of cyclocondensation reactions of **7**, we assessed a variety of mono/bis carbon electrophiles (1 or 2 equiv.; Scheme 6) for determining their electronic influence and nature under the optimized reaction conditions. Irrespective of the nature of aldehydes and ketones, the reaction was compatible with all kinds of substrates. Interestingly an α,β-unsaturated ketone *e.g.* benzalacetone when treated with **7** led to the formation of **1E10** *via* the PS reaction at the *C*-2 of imidazole as well as the aza-Michael addition at the β-carbon of benzalacetone. Fascinatingly reaction of an ester; methyl 4-oxobutanoate with **7** generated **1A3** (1D and 2D NMR; see the ESI†) which was formed as a result of the PS reaction followed by the formation of a five membered ring *via* the 5-*exo*-trig pathway due to a nucleophilic attack by the nitrogen atom on carbonyl ester. Substrate **7** on reaction with phenacyl chloride yielded **1E9** exclusively suggesting that the reaction proceeds *via* the imine pathway and not through nucleophilic substitution as no *N*-alkylated product was obtained. Similarly, reaction of **7** with phenyl isocyanate produced the corresponding PS product exclusively. Unfortunately, reaction of **7** with anhydrides such as maleic, phthalic and Boc_2O could only yield a nucleophilic adduct and failed to afford the corresponding PS products (see ESI, Scheme S1†).

On the other hand, **7** (1 equiv.) when reacted with $CH(OEt)_3$ (1 equiv.) using method B afforded a 7-membered endocyclised product; benzo[*f*]imidazo[1,5-*a*][1,3,5]triazepine (**2A1**; Scheme 7) exclusively and regioselectively. The structure of **2A1** was determined by 1D and 2D NMR experiments (1D and 2D NMR; see the ESI†). In the HMBC spectra of **2A1**, H-5 showed three-bond correlation with C-3a and H-6 (N) showed correlation with C-6a and C-10a (Scheme 7) and did not correspond to **16**.

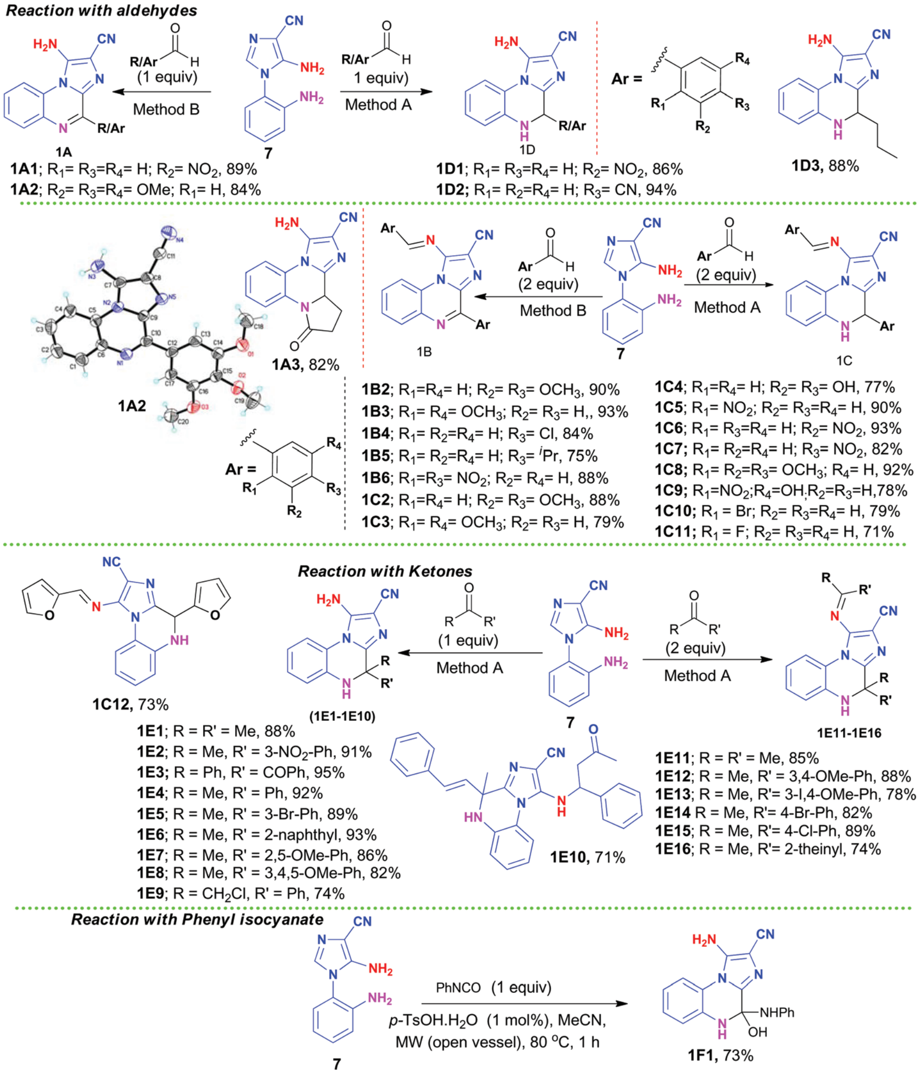
The regioselective formation of **2A1** can be reasoned by the initial attack by more nucleophilic nitrogen of **7** on acid activated $CH(OEt)_3$ followed by selective abstraction of more acidic protons of intermediate **V** (attributed to the CN group), leading to the product (Scheme 8). Similarly **7** (1 equiv.) when heated under MW (method B) with CDI (1 equiv.) in MeCN generated a cyclic urea **2A2** (Scheme 7). All the target compounds were new and characterized by mp, IR, NMR, HRMS and single crystal X-ray analysis (**1A2**) (Fig. S1†). Single crystal X-ray analysis confirmed the structure of compound **1A2**. The ORTEP diagram of **1A2** is provided in Scheme 6 with 50% probability displacement ellipsoids with atomic labeling.

With an intention to rationalize the experimental observation and to gain mechanistic insights into the formation of the 6-*endo-trig* product (**1-Me**/**1-Me1**) and 7-*exo-trig* product (**2A2**) from **7**, DFT[1,2] calculations were performed (Scheme 9). Formation of **1-Me** (with an acetaldehyde substrate) was found to be an endergonic process by 4.34 kcal mol^{-1} whereas it was endergonic by 11.18 kcal mol^{-1} for **1-Me1** (with a 3,4,5-trimethoxybenzaldehyde substrate). However, for the ease of calculations acetaldehyde was used as a model aldehyde. In the case of **2A2**, the reaction was found to proceed with the exergonic process by 20.12 kcal mol^{-1} indicating that 7-*exo-trig* cyclisation is energetically favourable.

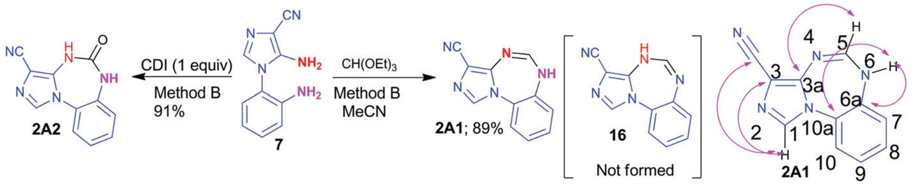
The mechanism for the formation of product **2A2** is shown in Scheme 10. The initial step involving the formation of the amide (**Int-A**) is exergonic by 8.05 kcal mol^{-1}. On the potential energy (PE) surface of the reaction, the transition state for the cyclization of **Int-A** could not be identified (with or without H_2O mediation), however, the transition state for the cyclization of the protonated **Int-A** could be found, in which water has been found to facilitate the proton transfer from the NH_2 group to the carbonyl oxygen. Hence, it is proposed that the



Scheme 5 Synthesis of **15**.



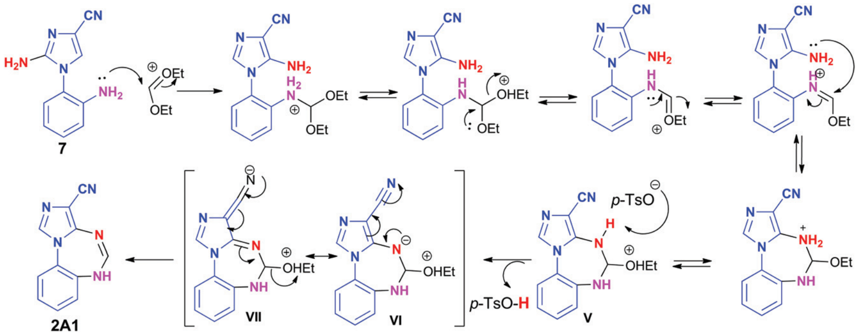
Scheme 6 Reactions of **7** with various aldehydes, ketones and phenyl isocyanate.



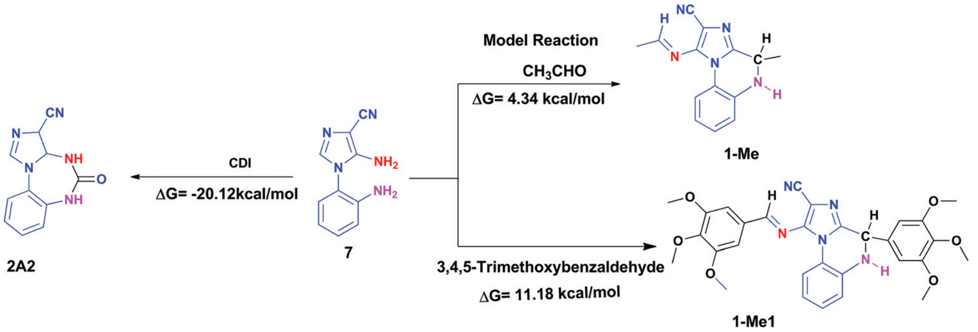
Scheme 7 Synthesis of the benzo[*f*]imidazo[1,5-*a*][1,3,5]triazepine ring system.

7-*exo-trig* cyclisation can take place under protonated conditions with the help of water. The cyclisation step is an endergonic process by 11.66 kcal mol^{-1} and the energy barrier for the cyclisation is 31.44 kcal mol^{-1}. Participation of water in the reaction helps in two ways: (i) in the proton exchange and (ii) in increasing the proximity of reactive centres (Schemes 10 and 11).

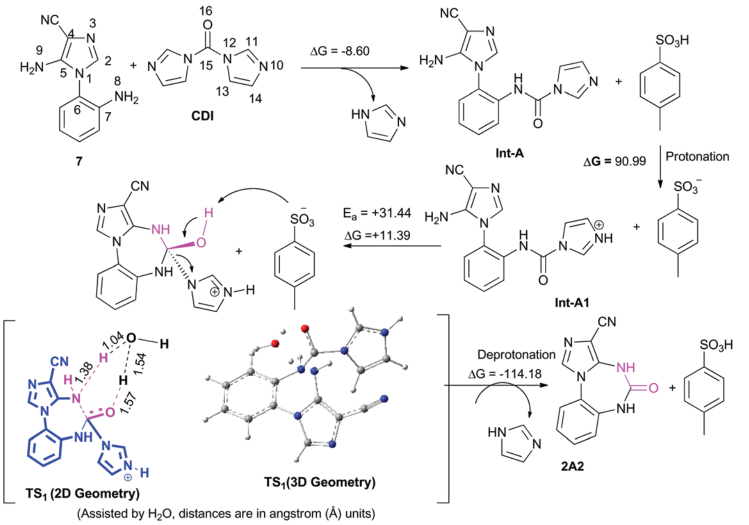
Although the PS reaction has been recently reported to involve the hydride transfer mechanism,[33] the formation of the product **1-Me** can be explained by invoking the participation of a carbene intermediate (**Int-C**, Scheme 12). Initially the reaction between **7** and acetaldehyde is expected to yield the intermediate **Int-B**, the formation of which is endergonic by 14.92 kcal mol^{-1}. This intermediate may undergo a 1,2-H



Scheme 8 Plausible mechanism of formation of **2A1**.

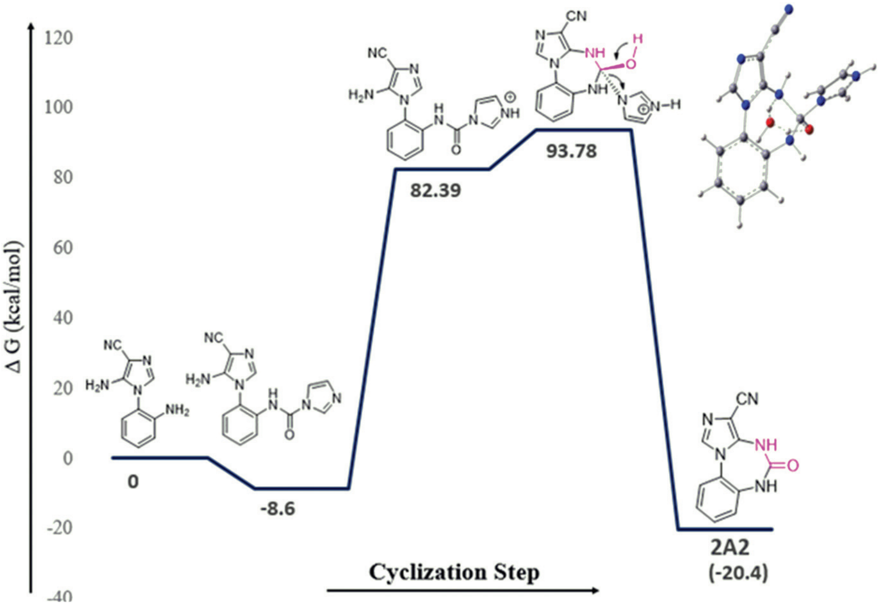


Scheme 9 Energetics for the formation of **2A2** and **1** from **7**.

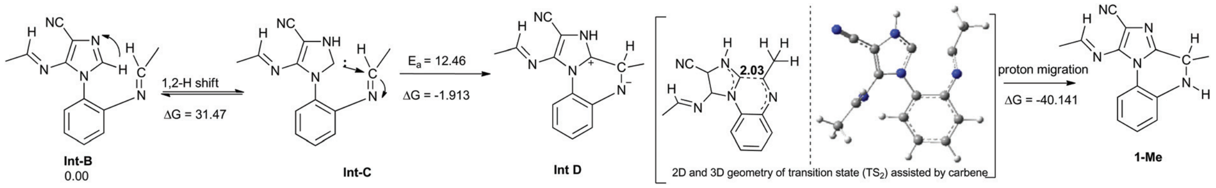


Scheme 10 A proposed pathway for the formation of **2A2**. The energy values are in kcal mol^{-1}. TS_1 represents the 2D and 3D geometries of the transition state assisted by H_2O. The distances are in angstrom (Å) units.

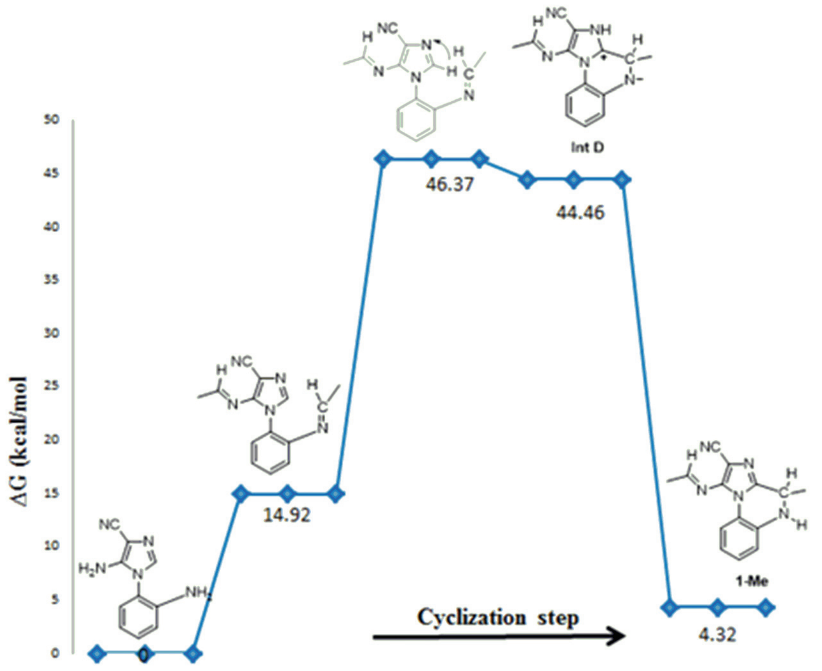
shift (presumably bimolecular) to provide the transient carbene intermediate **Int-C**, which is suitable for the cyclisation processes to yield the desired product. This process is endergonic by 31.46 kcal mol^{-1}. The cyclization (to give the transient intermediate **Int-D**) step is an exergonic process by 1.91 kcal mol^{-1}, and the energy barrier for the cyclisation is 12.46 kcal mol^{-1}. **Int-D** can undergo proton migration to give **1-Me**, which is an energetically favourable process



Scheme 11 The potential energy surface (PES) for the 7-*exo*-*trig* mechanism.



Scheme 12 Proposed pathway for the formation of **1-Me**. The scheme also represents the 2D and 3D geometries of the transition state (TS_2) assisted by carbene. The distance is given in angstrom (Å) units.



Scheme 13 The potential energy surface (PES) for the 6-*endo*-*trig* mechanism.

(Scheme 13). Attempts were made to identify a reaction mechanism which does not involve the participation of the carbene intermediate, but all the attempts failed to identify the appropriate intermediate and transition state structures on the PE surface. Hence, it is believed that the pathway proposed in Scheme 13 is feasible, especially because the reaction is carried out under microwave conditions.

Conclusions

In conclusion, we have synthesized a variety of undocumented imidazole fused quinoxaline and diazepines through a common precursor **7**. DFT calculations rationalized the formation of 6 *vs*. 7-membered products from **7** selectively based on the choice of reagents used. The present is the first case where NHC is suggested to be involved in the PS reaction mechanism. Further, the protocol delivers a straightforward method with high yields of a library of compounds of enormous interest in drug discovery without involving the use of heavy metals and strong acids.

Conflicts of interest

Authors do not declare any conflict of interest.

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