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Synthesis of functionalized pyrazolopyran derivatives: comparison of two-step *vs.* one-step *vs.* microwave-assisted protocol and X-ray crystallographic analysis of 6-amino-1,4-dihydro-3-methyl-4-phenylpyrano[2,3-c]pyrazole-5-carbonitrile

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Abstract. **A library of pyrazolopyran heterocycles was synthesized first by the traditional heating techniques using two-step and one-step procedures and then by microwave-assisted (MWA) multicomponent condensation of ethyl acetoacetate, hydrazine, malonodinitrile and a variety of substituted aldehydes. A comparison of the foregoing methods was first done based on the yields and then based on the time taken for the completion of the reactions. It was found that although the traditional methods gave slightly better yields, the MWA syntheses lead to substantial reduction in reaction timings. The title compound crystallizes in the triclinic crystal system with space group P–1. The crystal structure as elucidated by X-ray diffraction methods shows the presence of different intermolecular interactions, and the nature and energetics associated with these interactions have been characterized using PIXEL software.**

Keywords. **Heterocycles; multicomponent reaction; crystal structure; intermolecular interactions; PIXEL.**

1. Introduction

In an 'ideal synthesis', the variables that have to be optimized usually include time, cost, overall yield, simplicity of the procedure, safety issues and environmental compatibility. To achieve it, one can either recourse to the multistep sequential synthetic protocol or a more succinct one-pot reaction of three or more reactants in a multicomponent strategy. Thus, multicomponent reactions are now emerging as a responsible and environmentally benign alternative tool in organic synthesis,[1] and when seen from the perspective of the design of new and bioactive small organic molecules, their importance is all the more accentuated.[2] Additionally, the inclusion of multicomponent reaction protocols for organic heterocyclic synthesis has distinct green-chemistry[3] and atom-economy advantages.[4,5] Likewise, the increased use of microwave in organic synthesis is considerably reducing the generation of hazardous waste and reaction times,[6,7] thereby contributing to the greening of modern organic synthesis.

4H-Pyrans have been reported as the basic structural motifs for a gamut of useful compounds such as natural products.[8] Similarly, pyrazoles have also been reported as excellent starting materials for various bioactive small organic molecules.[9] Furthermore, pyrazole-fused pyrans (pyrazolopyrans) are well-established group of heterocyclic molecules possessing wide applications such as analgesic and CHK-1 inhibitor antitumour agents[10] to name a few.

The first report of synthesis of pyrazolopyrans was the reaction between 3-methyl-1-phenylpyrazolin-5-one and tetracyanoethylene.[11] Subsequently, other groups reported the synthesis of a series of 6-amino-5-cyano-4-aryl-4H-pyrazolo[3,4-b]pyrans.[12] Another three-component reaction between N-methylpiperidone, pyrazoline-5-one, and malonodinitrile was reported by Shestopalov and co-workers[13] although the reaction required heating or the use of electrochemical methods. The approach of Peng and co-workers[14] involved an interesting variation by encompassing the environmentally benign technology of microwave and ultrasound irradiation. Vasuki and Kumaravel reported a rapid four-component reaction in water.[15] Schlager *et al* disclosed a multistep synthesis of pyranopyrazoles starting with 1-phenylpyrazole.[16]

As is evinced by the preceding discussions, although many reported methods are available for the synthesis of the pyrazolopyran compounds but a clear and comprehensive comparative study was missing. It is with this

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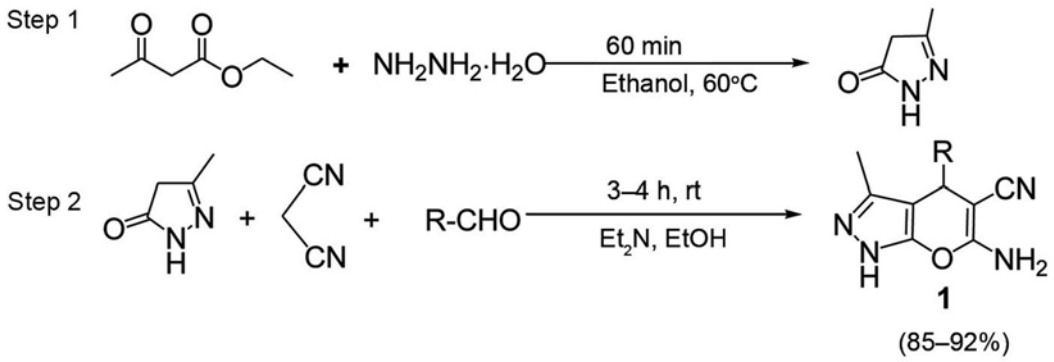
view in mind the simpler protocols for the preparation of the pyrazolopyrans were compared and evaluated. The idea was to evaluate and compare the two-step protocol under traditional and microwave heating *vs.* the one-step protocol under the traditional and microwave heating so as to obtain a more concrete idea of the reaction yields contrasted with the time of reactions.

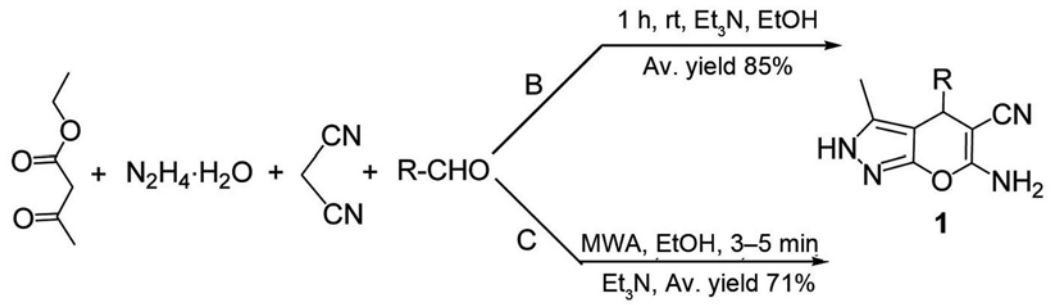
Initially, the well-established two-step methodology (method A) was tried[13] wherein active methylene compounds were first condensed with hydrazine hydrate to yield pyrazolinone. The latter compounds were isolated and then subjected to multicomponent condensation with malonodinitrile and various aldehydes to give the targeted pyrazolopyran compounds (scheme 1). Noticeably, the yields too were quite encouraging which is also corroborated with the previous reports.

Nevertheless, the overall time for the completion of the two-step reaction was 4–5 h. Keeping the latter handicap in mind, and the fact that most of the synthesized compounds were known, a one-step and greener multicomponent strategy (method B) to condense together all the four components (scheme 2) was evaluated.

Herein, to a stirred ethanolic mixture of hydrazine hydrate and ethylacetoacetate, the aldehyde, malononitrile and triethyl amine base were added successively at room temperature. Results showed that although the overall yields were decreased by about 10%, the reaction was over in an hour. Additionally, the reaction went smoothly at ambient temperatures. Although the scheme looks better in terms of reduced reaction timings, nevertheless the overall goal of greening of the organic synthetic methodology is still not fully achieved. Since green chemistry was always used as the guiding principle, it was decided to move towards microwave-assisted (MWA) synthesis (method C, scheme 3). Here, the one-step and two-step (not shown) procedures were again experimented. At this point, the mixture of the ketoester and hydrazine was stirred under microwave irradiation for a couple of minutes. Then, successive addition of the dicyano compound and the aldehyde was followed by the addition of the base. The overall sequence took less than 5–6 min. The two-step procedure once more gave better yields with reduced reaction timings. However, the one-step protocol turned out to be the fastest. Evidently this method, apart from being relatively environmentally nonthreatening, is also time saving while losing out only slightly on the yield front (table 1). It should be noted that the two procedures provide complementary choices in terms of fine tuning of yield *vs.* reaction timings. The comparative plots reveal the general picture of the conventional heating method *vs.* the MWA reactions. While figure 1 illustrates the relative reaction yields of the two methods, figure 2 portrays the time wise relationship between the two protocols. The plots clearly demonstrate



Scheme 1. Method A: the two-step protocol for synthesizing pyrazolopyrans.



Scheme 2. One-step protocols: method B (traditional heating) and method C (microwave-assisted synthesis).

Table 1. Synthesis of pyrazolopyrans.

	Method B[a]		Method C[b]	
Compound (R =)	(%)[c]	(*T*)[d]	(%)	(*T*)
2-Furanyl	92	270	62	5
4-Phenolic	84	120	78	4
3-Phenolic	81	120	65	4
4-Bromophenyl	79	210	66	5
3-Bromophenyl	83	210	57	5
3-Nitrophenyl	89	240	75	5
3-Thiophenyl	76	180	77	4
2-Pyrrolyl	88	180	75	4
3-Indolyl	91	210	79	5
2-Thiophenyl	93	210	80	5
4-Chlorophenyl	82	120	69	3
n-Butyl	68	270	59	5
2-Iodophenyl	93	240	73	5
Phenyl	90	210	81	4
4-Tolyl	84	120	88	3
2-Pyridyl	85	180	71	3
4-Pyridyl	88	180	70	3
3,4-Dimethoxyphenyl	78	120	85	2
2-Fluorophenyl	94	150	67	3
4-Nitrophenyl	77	240	73	5
4-Fluorophenyl	83	150	80	3
4-(N,N-dimethylamino)phenyl	90	120	78	3
2-Hydroxyphenyl	91	180	71	4
Methyl-1H-pyrazol-5(4H)-one	95	60	88	2

[a]Two-step, traditional heating. [b]One-step, microwave heating. [c]% Yields. [d]Time of reaction in minutes.

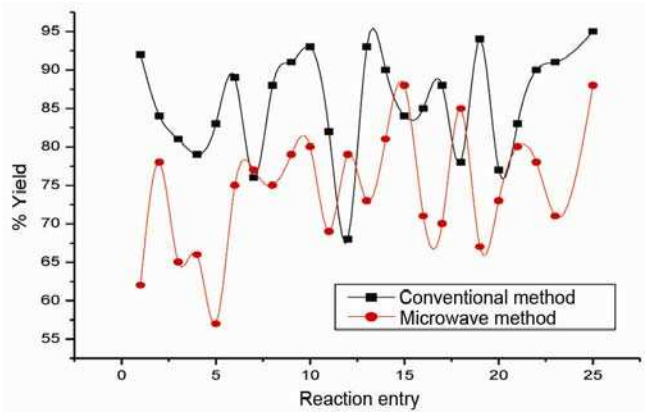


Figure 1. Plot of yields *vs.* the reaction entries under methods B and C.

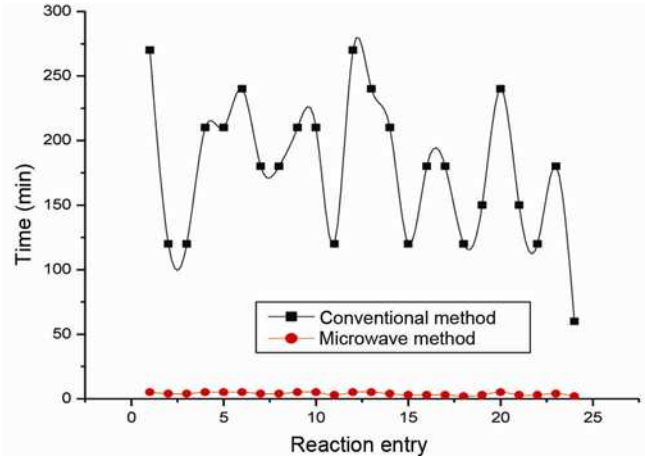


Figure 2. Plot of reaction times *vs.* the reaction entries under methods B and C.

that although the yields under methods B and C are comparable, the difference in their reaction times is quite significant. When the reaction standardization studies were performed, the results showed that among the solvents THF, acetone and water also gave reasonable yields while ethanol gave the best results in terms of both yields, and faster reaction rates. Similarly, among the different bases tried, triethyl amine proved to be the best.

To test the flexibility and adaptability of the procedures, a range of aldehyde functional groups were tried as shown in table 1. Markedly, both the protocols clearly seem to sustain an assortment of aldehydic substrates, including pyridyl, furanyl, thiophenyl, indolyl, straight-chain alkyl, phenolic and other variously substituted phenyl ones (table 1). All the compounds were characterized by the usual IR, NMR and melting point studies. The

structure of the compound in entry 15 (table 1) bearing the 4-tolyl group was fully established by single-crystal X-ray diffraction technique (CCDC no. 991567). The compound crystallizes in the triclinic space group and N–H···N hydrogen bonds link the adjacent molecules into linear chain motifs. The mechanism of the reaction was also of interest to us and therefore, we wanted to test an earlier proposed mechanism.[15] So, we first reacted 4-hydroxybenzaldehyde and malonodinitrile to obtain the Knoevenagel condensation product **2** (figure 3) *in-situ* whose ^{1}H NMR was recorded. This product was subsequently mixed with the 3-methyl-1H-pyrazol-5(4H)-one obtained separately by reaction of ethyl acetoacetate and hydrazine hydrate. The formation of the required pyrazolopyran product (entry 2, table 1) confirmed the proposed mechanism.

2. Experimental

2.1 *Synthesis*

2.1a *Method A:* Typical reaction procedure for the synthesis of pyranopyrazole at room temperature on magnetic stirrer (two-step): ethylacetoacetate (1 equiv.) was taken in sealed round bottom flask and mixed with ethanol (3 ml) with dropwise addition of hydrazine hydrate (1 equiv.). The mixture was allowed to stir for about 1 h at 60°C. The solid obtained was filtered and washed with distilled water and cold methanol and then recrystallized from ethanol. In another sealed round bottomed flask, the aldehyde (1.1 equiv.) and malonodinitrile (1.1 equiv.) were taken and mixed with 4 ml of ethanol with dropwise addition of triethylamine (1.5 equiv.). The mixture was allowed to stir for about 3–4 h at room temperature and then filtered and washed with water and then with a mixture of ethylacetate : hexane (20 : 80). The final pyrazolopyran compound was eventually recrystallized from ethanol.

2.1b *Method B (one-step):* The aldehyde (1.1 equiv.), malonodinitrile (1.1 equiv.) and triethylamine (1.5 equiv.) were added successively to about 4 ml of ethanol kept in a round bottomed flask at room temperature. The mixture was stirred vigorously for a few minutes. Then, ethylacetoacetate (1 equiv.) and hydrazine hydrate (1 equiv.) were added to the reaction mixture and the contents of the flask stirred for about 1 h. The solid precipitate was subjected to a similar work up as in method A.

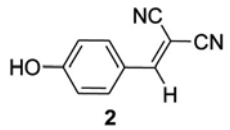


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Figure 3. Intermediate Knoevenagel condensation product **2**.

2.1c *Method C (MVA synthesis):* The reactants were added in the microwave in a similar fashion as in method B and stirred for about 5 min, filtered and analogous work up and purification done.

2.2 *Characterization*

The yield of the final product and the melting points of the compound were recorded. The synthesized compound was characterized by ^{1}H NMR (400 MHz, d_6-DMSO) δ: 12.09 (s, 1H), 7.06 (dd, J_1 = 6 Hz, J_2 = 18 Hz, 4H), 6.85 (s, 2H), 4.55 (s, 1H), 2.27 (s, 3H), 1.79 (s, 3H).^{13}C NMR (100 MHz, d_6-DMSO) δ: 176.1, 139.2, 135.1, 132.1, 129.0, 116.2, 59.2, 24.3, 21.5, 11.9. IR (KBr): 3403, 3332 (NH_2), 3029, 2208 (CN). The product obtained was further characterized by experimental X-ray diffraction technique.

2.3 *Data collection, structure solution and refinement*

Single-crystal X-ray diffraction data of the title compound was collected on *X'Calibur* CCD area detector diffractometer, Oxford Diffraction using MoKα radiation (λ = 0.7107 Å) at 293(2) K.[17] The crystal structure was solved by direct methods using SHELXS97[18] and refined by the full matrix least squares method using SHELXL97[18] present in the program suite WinGX.[19] All the non-hydrogen atoms are refined anisotropically and all the hydrogen atoms (except N1 H atoms) were geometrically fixed and allowed to ride on their parent C/N atoms with C–H = 0.93–0.98 Å and N–H distance of 0.86 Å. They were refined isotropically with U_{iso}(H) = 1.2U_{eq}(C) or 1.5U_{eq}(C) for methyl H atoms. An ORTEP view of the molecule indicating atom numbering scheme (thermal ellipsoids drawn at 40% probability level) is shown in figure 4. ORTEP diagram of the compound was generated using ORTEP32[20] and packing diagram was generated using PLATON[21] software. Geometrical calculations were performed using PLATON[21] and PARST.[22] Table 2 lists all crystallographic and refinement data. Intermolecular interactions are listed in table 3. PIXEL calculations were performed in order to estimate the nature and energies associated with the intermolecular interactions, which will enable to explore the role of these interactions in the stabilization of the crystal lattice.

2.4 *Theoretical calculations*

To get a better understanding of the contribution of intermolecular interactions to the crystal packing, it is important to get a quantitative evaluation of these interactions. Calculation of the lattice energy not only offers a possible way for polymorph prediction, but may also help

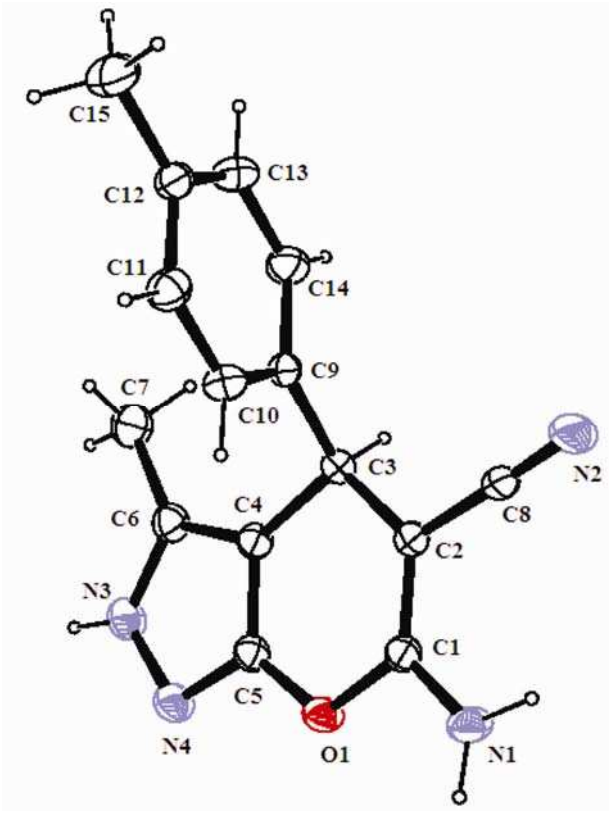

Figure 4. ORTEP view of the molecule with displacement ellipsoids drawn at 40%. H atoms are shown as small spheres of arbitrary radii.

Table 2. Crystallographic and refinement data.

CCDC no.	991567
Crystal description	Block
Crystal colour	White
Crystal size	$0.3 \times 0.2 \times 0.2$ mm^3
Empirical formula	$C_{15}H_{14}N_4O$
Formula weight	266.30
Radiation, wavelength	MoKα, 0.71073 Å
Unit cell dimensions	a = 6.3757(4), b = 9.8950(8), c = 10.6311(9) Å, α = 78.519(7)°, β = 84.605(7)° γ = 88.623(6)°
Crystal system	Triclinic
Space group	P–1
Unit cell volume	654.35(9) Å^3
No. of molecules per unit cell, Z	2
Temperature	293(2)
Absorption coefficient	0.089 mm^{-1}
F(000)	280
Scan mode	ω scan
θ Range for entire data collection	$3.61 < \theta < 26.00°$
Range of indices	h = –7 to 6, k = –11 to 12, l = –13 to 12
Reflections collected/ unique	4421/2561
Reflections observed ($I > 2\sigma(I)$)	1831
R_{int}	0.0239
R_{sigma}	0.0470
Structure determination	Direct methods
Refinement	Full-matrix least squares on F^2
No. of parameters refined	192
Final R	0.0467
$wR(F^2)$	0.1181
Weight	$1/[\sigma^2(F_o^2) + (0.0698P)^2 + 0.0000P]$ where $P = [F_o^2 + 2F_c^2]/3$
Goodness-of-fit	1.032
$(\Delta/\sigma)_{max}$	0.001 (for tors H15A)
Final residual electron density	$-0.229 < \Delta\rho < 0.239$ Å^{-3}

to understand the supramolecular chemistry and self-assembly during the nucleation and crystal growth processes and help to predict the melting and solubility behaviour of the compounds. The lattice energy of the title compound was calculated by PIXELC module in Couloumb–London–Pauli (CLP) computer program package (version 13.2.2012).[23] The total lattice energy is partitioned into its coulombic, polarization, dispersion and repulsion contributions (table 4). In CLP, the coulombic terms are handled by Coulomb's law while the polarization terms are calculated in the linear dipole approximation, with the incoming electric field acting on local polarizabilities and generating a dipole with its associated dipole separation energy; dispersion terms are simulated in London's inverse sixth power approximation, involving ionization potentials and polarizabilities; repulsion is presented as a modulated function of wave function overlap. All the stabilizing molecular pairs involved in crystal packing were selected from the mlc output file, which is generated after PIXEL energy calculations and were analysed with their interaction energies. The symmetry operator and centroid–centroid distance along with the coulombic, polarization, dispersion, repulsion and total interaction energies between the molecular pairs are presented in table 5. The molecular pairs are arranged in decreasing order of their stabilization energies. The PIXEL method has been preferred for the quantification of intermolecular interactions, primarily because of the following reasons: (1) It is computationally less demanding.[23] (2) It allows partitioning of total interaction energy into corresponding coulombic, polarization, dispersion and repulsion contribution, which facilitates a better understanding of the nature of intermolecular interactions contributing towards the crystal packing.[24] (3) The energies obtained from PIXEL calculation are generally comparable with high level quantum mechanical calculations.[25,26]

3. Results and discussion

The compound 6-amino-1,4-dihydro-3-methyl-4-phenylpyrano[2,3-c]pyrazole-5-carbonitrile crystallizes in the triclinic crystal system with space group P–1. The

Table 3. Intermolecular hydrogen bonding (e.s.d.'s in parentheses).

D–H···A	D–H (Å)	H···A (Å)	D···A (Å)	D–H···A (deg)	Symmetry code
N1–H1···N2	0.92(2)	2.23(2)	3.147(3)	174(1)	$-x, -y + 1, -z + 1$
N1–H2···N4	0.92(2)	2.33(2)	3.169(2)	171(2)	$-x + 1, -y + 1, -z$
C15–H15C···N2	0.96	2.57	3.352(3)	139	$-x - 1, -y, -z + 1$

Table 4. Lattice energy from CLP (in kcal mol^{-1}).

	E_{Cou}	E_{Pol}	E_{Disp}	E_{Rep}	E_{Tot}
Molecule 1	–22.90	–10.25	–38.26	30.64	–40.77

Table 5. PIXEL interaction energies (I.E.) (kcal mol^{-1}) between molecular pairs related by a symmetry operation and the associated intermolecular interactions in the crystal.

Motif	Centroid distance (Å)	E_{Cou}	E_{Pol}	E_{Disp}	E_{Rep}	E_{Tot}	Symmetry	Important interactions
1	9.438	–14.58	–5.38	–4.35	10.16	–14.15	$-x, 1 - y, 1 - z$	N1–H1···N2
2	6.542	–5.88	–5.45	–12.55	10.78	–13.10	$-x, -y, -z$	N3–H3A···Cg1 N3–H3A···C15 C7–H7C···C6
3	9.069	–11.38	–4.78	–5.19	8.72	–12.62	$1 - x, 1 - y, -z$	N1–H2···N4 O1···O1
4	6.088	–1.67	–1.22	–12.59	7.72	–7.77	$-x, 1 - y, -z$	C14–H14···O1 C3–H3···O1
5	7.276	–2.44	–1.07	–8.96	4.92	–7.52	$-x, -y, 1 - z$	C15–H15A···N1 C11–H11···C10
6	6.376	–2.22	–1.15	–7.40	3.78	–7.03	$-1 + x, y, z$	C7–H7B···N4
7	8.907	–3.89	–1.91	–7.60	7.74	–5.66	$-1 - x, -y, 1 - z$	C15–H15B···N2

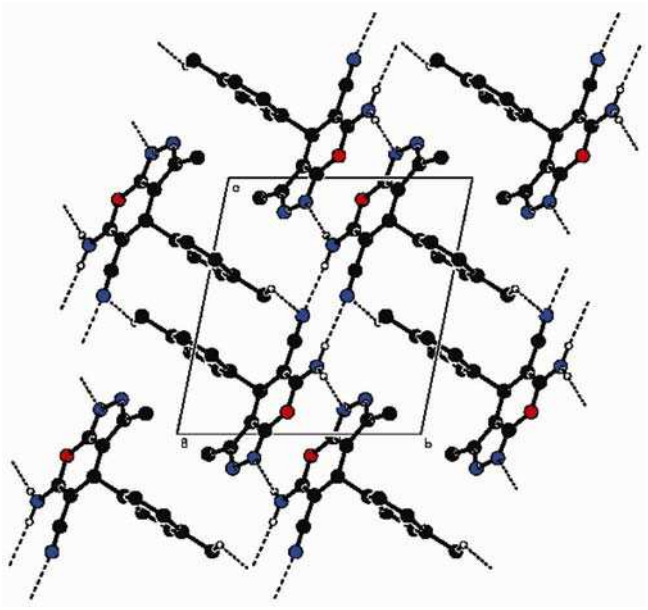

Figure 5. The crystal packing of the title compound viewed down the *a*-axis, showing intermolecular hydrogen bonding interactions as dashed lines.

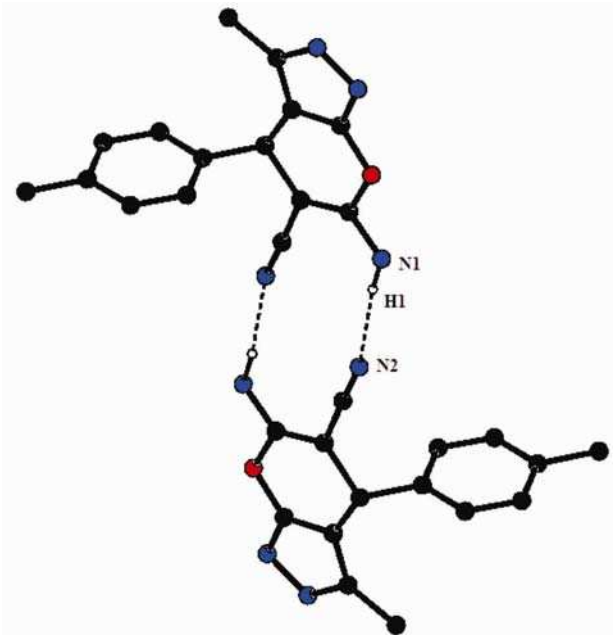

Figure 6. View of R^2_2 (12) ring motifs formed by N–H···N interaction between two molecules.

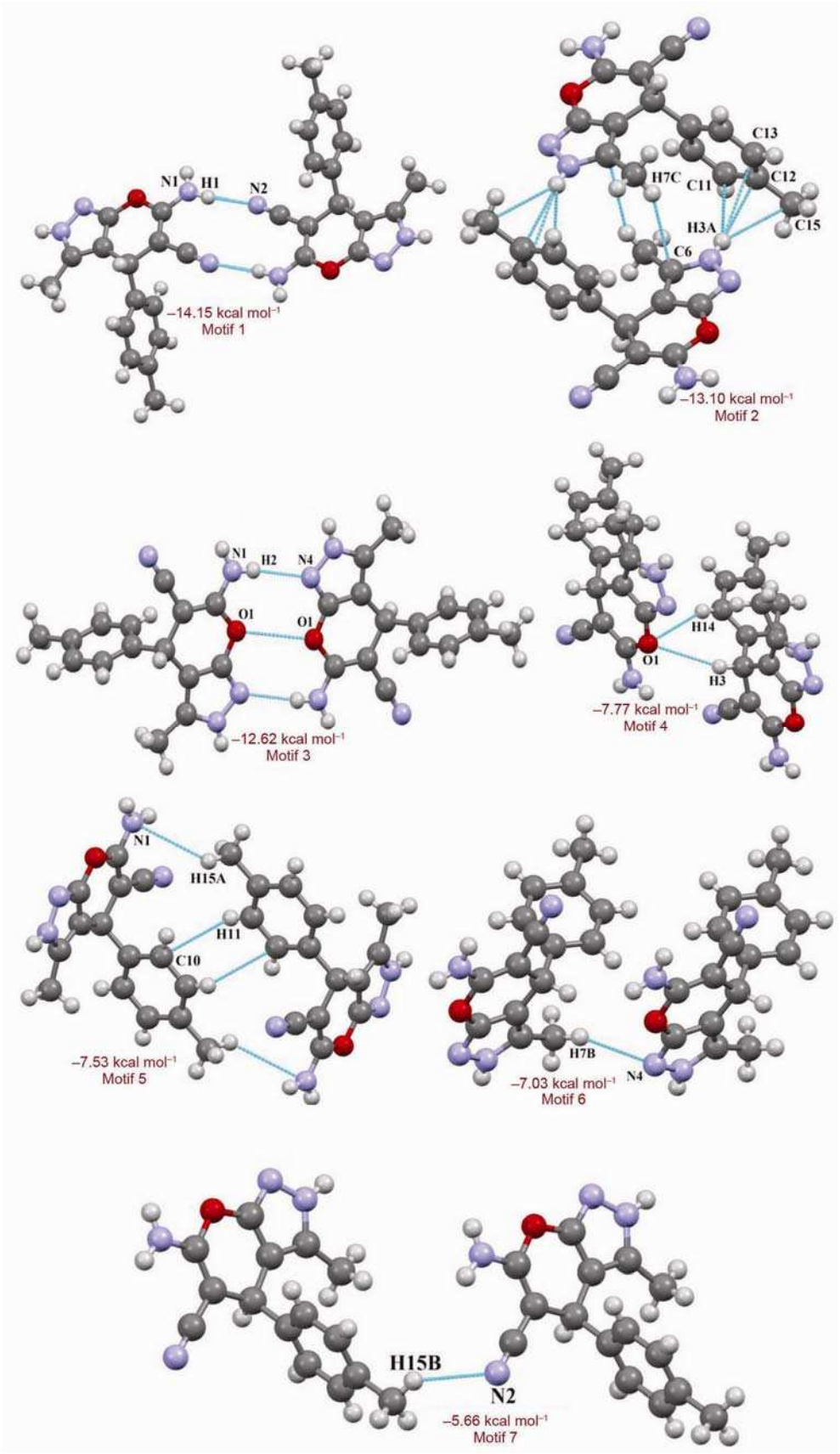

Figure 7. Molecular pairs (1–7) with their interaction energies.

molecule comprises of a pyrazole, pyran and a tolyl ring (figure 4). The bond distances in the title compound are within normal ranges[27] and comparable to the closely related structures.[28,29] The dihedral angle between the tolyl ring and the pyrazole ring is 86.46(5)° and between the tolyl and pyran ring is 84.07(5)°. The dihedral angle between the mean planes of the pyrazole and pyran ring is 2.39(6)°, which confirms their coplanar character. All the rings are planar with a maximum deviation of 0.003(2) Å for the tolyl C11 atom, –0.002(2) Å for the pyrazole C5 atom and 0.022(2) Å for the pyran C3 atom. The carbonitrile group exhibits linearity, a feature commonly observed in carbonitrile compounds.[30]

Two N–H···N and one C–H···N intermolecular hydrogen bond interactions (figure 5) are observed for maintaining the crystal packing, in which the N1–H1···N2 intermolecular interactions are observed to form $R^2_2(12)$ ring motifs[31] (figure 6). Details of intermolecular hydrogen bonds are given in table 3.

The lattice energy calculation for the title compound is given in table 4. Molecular pairs of the title compound extracted from crystal structure along with their respective interaction energies are shown in figure 7. The maximum stabilization to the crystal structure comes from N–H···N intermolecular interaction involving H1 with N2. The stabilization energy of this pair is, –14.15 kcal mol^{-1}, obtained using PIXEL and the interaction is mainly coulombic in nature. The next most stabilized pair shows the presence of bifurcated donor atom N3 involving H3A with Cg1 and C15, along with this interaction the molecular pair also shows the presence of C–H···C interaction (involving H7C with C6) and hence form dimer. The stabilization energy of this pair is –13.10 kcal mol^{-1}. Molecular pair 3 shows the presence of N–H···N interaction (involving H2 with N4) and O1···O1 interaction, resulting in a stabilization energy of –12.62 kcal mol^{-1}. Another molecular pair (Motif 4) shows the presence of bifurcated acceptor atom O1 with H3 and H14 having interaction energy of –7.77 kcal mol^{-1} with major contribution from dispersion component. The next most stabilized molecular pair involves C–H···N and C–H···C hydrogen bonding involving H15A interacting with N1 and H11 interacting with C10, respectively, with an interaction energy of –7.53 kcal mol^{-1} and the stabilization mainly comes from dispersion component. Molecular pairs 6 and 7 show the presence of C–H···N interaction involving H7B with N4 and H15B, with N2 having interacting energies of –7.03 and –5.66 kcal mol^{-1}, respectively, providing additional stabilization to the crystal packing. The combined nature of these interactions is mainly dispersive in nature.

4. Conclusions

A series of pyrazolopyran-based molecules via the traditional and the microwave heating methodologies have been prepared. The synthetic approaches were compared based on the total yields of the reactions and their overall run time. The results thus obtained reveal that the two protocols are complementary to each other and the microwave scheme offers a huge gain in terms of the reaction timings, atom economy and environmental friendliness. Crystallographic analysis and energy calculations shows the presence of different key structural motifs, which aid in the stabilization of crystal packing. Analysis of different structural motifs shows that weak intermolecular interactions are also the major contributors that stabilizes the crystal packing in addition to strong interactions. This demonstrates that the calculation of lattice energies is a useful approach to assess the stability of molecular crystals, in which dispersion type interactions make up an essential part of the intermolecular interactions.

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