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Synthesis of 1-aroyl-3-methylsulfanyl-5-amino-1,2,4-triazoles and their analysis by spectroscopy, X-ray crystallography and theoretical calculations



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ABSTRACT

N-Aroyl-1,2,4-triazoles TAM and TACl were regioselectively synthesized in excellent yields through an efficient N-acylation reaction of 3-amino-5-methylsulfanyl-1H-1,2,4-triazole with aroyl chlorides. Structures of N-aroyl-1,2,4-triazoles were studied by single-crystal X-ray diffraction, observing that their crystal structures are characterized by the formation of dimers through N-H…N bonds. The supramolecular assembly depends on the sort of connections between dimers, which notably change with the parasubstituent on the aroyl group. The directly calculated ionization potential (IP), electron affinity (EA), electronegativity (χ), electrophilicity index (ω), hardness (η), and chemical potential (μ) are correlated with the HOMO and LUMO orbital energies. Moreover, molecular electrostatic potential maps of both molecules have been calculated showing a negative region at N2 atom of the 1,2,4-triazole ring instead of exocyclic amino group. The vibrational spectral analysis was carried out using infrared spectroscopy in the range 4000–400 cm^{-1} for N-aroyl-1,2,4-triazoles TAM and TACI. The experimental spectra were recorded in the solid state. The fundamental vibrational frequencies and intensity of vibrational bands were evaluated using density functional theory (DFT) with the standard B3LYP/6-31G(d,p) method and basis set yielding fairly good agreement between observed and calculated frequencies. Simulation of infrared spectra utilizing the results of these calculations led to an excellent overall agreement with the observed spectral patterns.

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1. Introduction

Amide group is one of the most important chemical building blocks found in nature and is also part of a vast number of synthetic structures. This structural unit constitutes the backbone of peptides, proteins, bioactive compounds, commercial drugs, agrochemicals, and polymers [1,2]. The classical amide moiety formation is among the most executed procedures in the chemistry and pharmaceutical industry. From the viewpoint of atom economy and environmental sustainability, the amide bond construction by operationally simple, efficient, eco-friendly, and chemoselective methodologies is still in great demand [1-4].

Among the broad range of privileged structures, 1,2,4-triazole represents one of the most prominent classes of N-heterocyclic scaffolds for drug discovery due to its wide range of biological and pharmacological properties such as analgesic [5], antiviral [6,7], antimicrobial [8], antifungal [9,10], antihypertensive [11], and anticancer [12]. Furthermore, the use of 1,2,4-triazole derivatives containing an amine group enables the preparation of highly functionalized triazole-based compounds with interesting biological activities [13,14]. For example, amino-1,2,4-triazoles are amenable to further derivatization via palladium-catalyzed Buchwald-Hartwig amination [15,16], and N-acylation reaction [17]. Particularly, Nacyl-1,2,4-triazoles are still highly desirable due to their high selectivity towards pharmacological targets, including cells infected with the rubella virus [18,19], inhibitors of CDK1 and CDK2 [20], and Microsomal Triglyceride Transfer Protein (MTP) inhibitors useful in the treatment of atherosclerosis [21]. Although diverse synthetic methods have been developed for the synthesis of amide-

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Scheme 1. Chemo and regioselective acylation reaction of 3-amino-5-methylsulfanyl-1H-1,2,4-triazole (1) with aroyl chlorides (2).

containing 1,2,4-triazoles, there remains a great need to find operationally simple and sustainable methodologies for the chemo- and regioselective *N*-acylation reaction of 3-amino-5-methylsulfanyl-1*H*-1,2,4-triazole.

In connection with the ongoing development of efficient protocols for amide bond construction [17], and our continuing interest in the search of simple and greener methods for the synthesis of biologically active *N*-heterocycles [22–25], we envisioned that the chemo- and regioselective *N*-acylation of 3-amino-5-methylsulfanyl-1*H*-1,2,4-triazole (1) with aroyl chlorides 2a-b would provide the 5-amino-3-(methylthio)–2,5-dihydro-1*H*-1,2,4-triazol-1-yl)(*p*-tolyl)methanone (3a, TAM) and 5-amino-3-(methylthio)–2,5-dihydro-1*H*-1,2,4-triazol-1-yl)(4-

chlorophenyl)methanone (3b, TACl) using triethylamine as a base in the absence of any additive or catalyst (Scheme 1). In this work, the structures of *N*-aroyl-1,2,4-triazoles TAM and TACl (Scheme 1) were investigated using X-ray crystallography and both theoretical and spectroscopic studies.

2. Experimental

2.1. General information

All reagents were purchased from commercial sources and used without further purification unless otherwise noted. All starting materials were weighed and handled in air at room temperature. The reactions were monitored by TLC visualized by UV lamp (254 nm or 365 nm). Flash chromatography was performed on silica gel (particle size 0.040-0.063 mm). NMR spectra were recorded at 400 MHz (¹H) and 101 MHz (¹³C) at 298 K using tetramethylsilane (0 ppm) as the internal reference. NMR spectroscopic data were recorded in CDCl₃ using as internal standards the residual non-deuterated signal for ¹H NMR and the deuterated solvent signal for ¹³C NMR spectroscopy. DEPT spectra were used for the assignment of carbon signals. Chemical shifts (δ) are given in ppm and coupling constants (J) are given in Hz. The following abbreviations are used for multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, and m = multiplet. Melting points were determined using a capillary melting point apparatus and are uncorrected. The FT-

IR spectra of the 1,2,4-triazole-based amides were measured in the region 4000-600 cm⁻¹ using a SHIMADZU IR Affinity-1 spectrophotometer (equipped with an ATR accessory). Spectra are reported in wavenumber (cm⁻¹) and only selected resonances are reported. Mass spectra were recorded on a Shimadzu-GCMS 2010-DI-2010 spectrometer (equipped with a direct inlet probe) operating at 70 eV. UV-Vis absorption spectra were recorded in methanol (50 μ M) at 298.15 K on a Thermo Scientific Evolution 220 UV-Vis spectrophotometer using a peltier control and a cooling unit PCCU1. The X-ray intensity data were measured at room temperature, 298 (2) K, using MoK α radiation ($\lambda = 0.71073$ Å) in an Agilent SuperNova, Dual, Cu at Zero, Atlas four-circle diffractometer equipped with a CCD plate detector. The collected frames were integrated with the CrysAlis PRO software package [26]. Data were corrected for the absorption effect using the CrysAlis PRO software package by the empirical absorption correction using spherical harmonics, implemented in the SCALE3 ABSPACK scaling algorithm [26]. The structures of TAM (3a) and TACl (3b) were solved using an iterative algorithm [27], and then completed by difference Fourier map.

2.2. Synthesis

2.2.1. Regioselective synthesis of

1-(aroyl)–3-methylsulfanyl-5-amino-1,2,4-triazole 3a-b

The corresponding aroyl chloride 2a-b (2.0 mmol) was added dropwise to a solution of 3-amino-5-methylsulfanyl-1*H*-1,2,4-triazole (1) (2.0 mmol) and triethylamine (2.4 mmol) in dichloromethane (5.0 mL) (Scheme 2). The mixture was stirred at 298 K for 1 h until the starting materials were no longer detected by thin-layer chromatography. After the solvent was removed under reduced pressure, water (5.0 mL) was added, and the aqueous solution was extracted with ethyl acetate (2 × 5.0 mL). The combined organic layers were dried with anhydrous magnesium sulfate, and the solvent was removed under reduced pressure to afford the crude compound. Ultimately, the crude product was purified by flash column chromatography on silica gel using CH₂Cl₂/MeOH (30:1, v/v) as eluent to afford pure *N*-aroyl-1,2,4-triazoles 3a-b. Single crystals of both compounds suitable for diffraction analysis were grown via slow evaporation from



(i) Et₃N (1.2 equiv), DCM, 298 K, 1 h. TAM and TACI are abbreviations for *N*-aroyltriazoles 3a-b.

Scheme 2. Synthesis of 1-(aroyl)-3-methylsulfanyl-5-amino-1,2,4-triazoles 3a-b.

methanol at room temperature under ambient atmosphere. Although *N*-aroyl-1,2,4-triazoles 3a-b were synthesized three decades ago [19,28]; the structural and electronic information obtained from spectroscopic, crystallographic, and DFT quantum-chemical analysis has not been reported.

2.2.2. 1-(4-Methylbenzoyl)–3-methylsulfanyl-5-amino-1,2,4-triazole (3a, TAM)

Following the general procedure, the reaction of 1 (260 mg) with 4-methylbenzoyl chloride (2a) (264 µL) and triethylamine (334 µL) afforded amide TAM (3a) as a white solid [462 mg, 93% yield, m.p. 461–462 K (amorphous)]. Lit. 459–461 K [19]. Rf (CH₂Cl₂/MeOH: 30/1) = 0.36. Recrystallization of TAM (3a) from methanol afforded crystalline white prisms suitable for single-crystal X-ray diffraction analysis. ¹H NMR (400 MHz, CDCl₃): δ = 2.43 (s, 3H, CH₃), 2.53 (s, 3H, SCH₃), 6.91 (br s, 2H, NH₂), 7.28 (d, *J* = 8.0 Hz, 2H, Ar–H), 8.15 (d, *J* = 8.0 Hz, 2H, Ar–H) ppm. ¹³C{¹H} NMR (101 MHz, CDCl₃): δ = 13.7 (SCH₃), 21.8 (CH₃), 128.9 (CH), 131.6 (Cq), 131.6 (CH), 144.4 (Cq), 158.9 (Cq), 162.5 (Cq), 167.5 (Cq) ppm. The UV–Vis spectra of 3a (50 µM) was obtained in methanol with a λ_{max} at 248 nm and 289 nm. MS (70 eV) *m/z* (%): 248 (12, M⁺), 119 (100), 91 (91), 74 (29), 65 (52) (see Supporting Information).

2.2.3. 1-(4-Chlorobenzoyl)–3-methylsulfanyl-5-amino-1,2,4-triazole (3b, TACl)

Following the general procedure, the reaction of 1 (260 mg), 4chlorobenzoyl chloride (2b) (256 µL) and triethylamine (334 µL) afforded compound TACl (3b) as a white solid [520 mg, 97% yield, m.p. 458 K (amorphous)]. Lit. 448–450 K [28]. Rf (CH₂Cl₂/MeOH: 30/1) = 0.28. Recrystallization of TACl (3b) from methanol afforded crystalline white prisms suitable for single-crystal X-ray diffraction analysis. ¹H NMR (400 MHz, CDCl₃): δ = 2.53 (s, 3H, SCH₃), 6.84 (br s, 2H, NH₂), 7.46 (d, *J* = 8.4 Hz, 2H, Ar–H), 8.21 (d, *J* = 8.4 Hz, 2H, Ar–H) ppm. ¹³C{¹H} NMR (101 MHz, CDCl₃): δ = 13.7 (SCH₃), 128.5 (CH), 130.0 (Cq), 132.9 (CH), 140.0 (Cq), 159.0 (Cq), 163.2 (Cq), 166.5 (Cq) ppm. The UV–Vis spectra of 3b (50 µM) was obtained in methanol with a λ_{max} at 248 nm and 304 nm. MS (70 eV) *m/z* (%): 270/268 (9/24, M⁺), 141/139 (32/100), 113/111 (34/94), 85 (27), 75 (67) (see Supporting Information).

2.3. Computational study

The geometry optimization of the 1-(aroyl)-3-methylsulfanyl-5-amino-1.2.4-triazoles 3a-3b was performed using Density Functional Theory (DFT) Becke's three-parameter hybrid function with the non-local correlation of Lee-Yang-Parr (B3LYP) method at 6-31G(d,p) basis set [29-31]. A linear regression analysis using results from two basis sets 6-31G(d,p) and 6-311+G(d,p) showed that the base 6–31G(d,p) achieved a better behavior in the analysis of the properties of these compounds with a minor computational cost (see Supporting Information). The corresponding harmonic vibrational frequencies were computed at the same level of theory to characterize them as minima (no imaginary frequencies) using the Gaussian09 package program [32], and the zero-point energy (ZPE) corrections were also performed at the same level of theory. The assignment of the calculated frequencies was carried out based on potential energy distribution (PED) analysis, using the "Vibrational Energy Distribution Analysis" (VEDA4) program [33], and the vibrations were visualized with the program Gauss View 5.0.8 [34]. The DFT calculations have sought to establish the stability of synthesized 1,2,4-triazole-based amides with the help of quantum chemical descriptors such as Frontier molecular orbitals, HOMO-LUMO energy gap, and global reactivity descriptors such as potential (IP), electron affinity (EA), electrophilicity index (ω) , chemical potential (μ) , electronegativity (χ) and hardness (η) . The molecular electrostatic potential analysis is presented as a powerful tool for the knowledge of charge distribution and its results can be useful in determining how molecules interact with each other. The *multiwfn* algorithm was used for these calculations [35]. The electronic absorption spectra were obtained from TD-DFT calculations using the same method and level of theory used to estimate the vibrational frequencies and the integrated integral equation formalism for the polarizable continuum model (IEFPCM) was applied to consider solvent effects in the calculation.

2.4. Refinement and data collection strategy

Crystal data, data collection, and structure refinement details are summarized in Table 1. The X-ray intensity data were measured at room temperature [298 (2) K] using CuK α radiation $(\lambda = 1.54184 \text{ Å})$, and ω scans, in an Agilent SuperNova, Dual, Cu at Zero, Atlas four-circle diffractometer equipped with a CCD plate detector. The collected frames were integrated with the CrysAlis PRO software package (CrysAlisPro 1.171.39.46e, Rigaku Oxford Diffraction, 2018). Data were corrected for the absorption effect using the CrysAlis PRO software package by the empirical absorption correction using spherical harmonics, implemented in the SCALE3 AB-SPACK scaling algorithm. The final anisotropic full-matrix leastsquares refinements on F² with 163, and 161 variables converged at R1 = 5.3%, and 3.5% for the observed data, and R2 = 13.7%and 9.2% for all data. The goodness-of-fit was 1.07 and 1.04 for TAM (3a) and TACI (3b), respectively. The largest peaks in the final difference electron density synthesis were $0.253/0.304 \text{ e}^{-}/\text{Å}^{3}$, and the largest holes were -0.248/-0.271 e⁻/Å³ with RMS deviations of $0.05/0.04 \text{ e}^{-}/\text{Å}^{3}$, respectively. Table 1 shows the number of measured reflections (the total number of intensities, excluding reflections that are classed as systematically absent arising from translational symmetry), independent reflections (include Friedel-equivalent reflections, i.e. symmetry-equivalent under Laue symmetry but inequivalent under crystal class), and observed reflections (significantly intense, satisfying the criterion specified by $I > 2 \sigma(I)$ and may include Friedel-equivalent reflections) (see dictionary at enCIFer version1.51.).

All the non-hydrogen atoms were refined anisotropically, while the hydrogen atoms were generated geometrically, placed in calculated positions (C–H = 0.93-0.96 Å), and included as riding contributions with isotropic displacement parameters set at 1.2 - 1.5times the U_{eq} value of the parent atom. H atoms belonging to N– H groups were located in difference density maps and were refined freely. The crystal structures were refined using the program SHELXL2014 [36]. Molecular and supramolecular graphics were carried out using the software Mercury [37]. Single crystals of *N*aroyl-1,2,4-triazoles 3 suitable for diffraction analysis were grown via slow evaporation from methanol at room temperature under ambient atmosphere.

3. Results and discussion

3.1. Synthesis of 1-(aroyl)–3-methylsulfanyl-5-amino-1,2,4-triazole 3a-b

The synthesis of amide-containing *N*-heterocyclic compounds has received augmented interest over the past decades due to their broad range of applications in medicinal chemistry, drug design, and the pharmaceutical industry. The most traditional and simple procedure for the synthesis of an amide consists of a nucleophilic acyl substitution between an aroyl chloride and an amine in the presence of a base [17,22]. Applying this procedure to the stirring of an equimolar mixture of the *NH*-1,2,4-triazole 1 and 4methylbenzoyl chloride (2a) in dichloromethane as solvent and tri-

Crystallographic data of TAM (3a) and TACl (3b).

Crystal Data	TAM (3a)	TACI (3b)
Chemical Formula	$C_{11}H_{12}N_4OS$	C ₁₀ H ₉ ClN₄OS
Mr	248.31	268.72
Melting point, K	461	458
Solvent for Crystallization	Methanol	Methanol
Crystalline system, space group	$P2_1/n$	P-1
a, b, c (Å)	5.3866(10), 9.0145(17), 24.833(5)	7.0207(8), 7.6989(9), 12.2124(11)
α, β, γ (°)	90, 92.427(19),90	86.682(9), 87.439(8), 64.728(11)
Volume, (Å ³)	1204.7(4)	595.77(12)
ρ , kg m ⁻³	1.369	1.498
Z	4	2
Temperature, (K)	298	298
Radiation type	Mo K $_{\alpha}$	Mo K $_{\alpha}$
$\mu \text{ (mm}^{-1})$	0.258	0.484
Crystal size (mm)	0.38, 0.31, 0.29	0.35, 0.28, 0.24
Theta range for data collection	3.254 to 27.564	3.210 to 27.093
Index range	-6<=h<=6, -11<=k<=11, -31<=l<=31	-8<=h<=8, -9<=k<=9, -15<=l<=15
Data collection		
Diffractometer	Agilent SuperNova Dual Source diffractometer with	Agilent SuperNova Dual Source diffractometer with
	an Atlas detector	an Atlas detector
Absorption correction	Multi-scan (CrysAlis PRO; Agilent, 2014)	Multi-scan (CrysAlis PRO; Agilent, 2014)
Tmin, Tmax	0.298, 1.000	0.711, 1.000
No. of measured, independent and observed	13,397, 2643, 2189	12,964, 2615, 2290
reflections $[I>2\sigma(1)]$		
R _{int}	0.072	0.031
Refinement		
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.053, 0.137, 1.07	0.035, 0.092, 1.04
No. of reflections	2189	2290
Refined parameters	163	161
H-atoms treatment	H atoms treated by constrained refinement	H atoms treated by constrained refinement
$\Delta ho_{ m max}$, $\Delta ho_{ m min}$ (e Å ⁻³)	0.253, -0.248	0.304, -0.271

ethylamine (1.2 equiv) as base at 298 K for 1 h, regioselectively afforded the amide TAM (3a) in 93% isolated yield. Rewardingly, the scope of aroyl chloride substrates was extended to 4-chlorobenzoyl chloride (2b) leading to the expected amide TACI (3b) in 97% isolated yield. This chemo- and regioselective synthesis of 3a-b was distinguished by its operational simplicity, high yielding, and the absence of any drying agent under normal atmospheric conditions. Albeit these 1,2,4-triazole-based amides 3a-b were previously synthesized three decades ago [19,28], the structural and electronic information obtained from spectroscopic, crystallographic, and DFT quantum-chemical analysis has not been reported. For that reason, TAM (3a) and TACI (3b) were initially characterized by spectroscopic techniques (NMR, FT-IR, and UV–Vis) and mass spectrometry (see Experimental section and Supporting Information).

The presence of two absorption bands in the range of 3419-3431 cm^{-1} and 3275–3278 cm^{-1} assigned to the $-\text{NH}_2$ functionality, and one absorption band in the range of 1674-1680 cm⁻¹ assigned to the newly NC=O functionality, are the most relevant features of the FT-IR spectra. The absence of the triazolic NH proton and the presence of a broad singlet at 6.91 ppm and 6.84 ppm for TAM (3a) and TACl (3b), respectively, assigned to the -NH₂ proton in the ¹H NMR spectra, and the presence of the newly NC=O functionality at 167.5 ppm and 166.5 ppm for TAM (3a) and TACl (3b), respectively, in the ¹³C NMR spectra, suggest that the nucleophilic acyl substitution occurred chemo- and regioselectively on the N2 atom of the 1,2,4-triazole ring instead of the exocyclic amino group (-NH₂). The most relevant feature in the EI-MS spectra for the 1,2,4-triazole-based amides TAM (3a) and TACl (3b) correspond to a base peak assigned to the respective stable acylium ions (see Supporting Information).

3.2. X-ray crystallographic analysis

The collected crystal data and structure refinement details of TAM (3a) and TACI (3b) are summarized in Table 1, and the respective molecular structures are shown in Fig. 1. Both molecules

are characterized by two main planes that constitute the complete molecular structures (Fig. 1). The dihedral angles between the weighted least-squares mean planes that contain the phenyl and triazole rings are 31.94 ° and 32.59 ° for TAM (3a) and TACl (3b), respectively (Fig. 1), showing a slight difference in their conformations. The different substituting groups in the phenyl ring, – CH₃ and –Cl, have no structural effects over the molecules. Bond distances such as C10–C8 (~1.48 Å), C8–N4 (~1.39 Å), and N7–C5 (~1.32 Å) are equivalents in both structures. A complete report of the bond lengths and bond/valence angles for TAM (3a) and TACl (3b) is shown in the Supporting Information.

In order to obtain a better understanding of the crystal packing, the crystallographic analysis was complemented with calculations using CE-B3LYP energy model based on B3LYP/6-31G(d,p) quantum mechanical charge distribution for unperturbed monomers which was applied to the molecular crystals. This model is implemented in CrystalExplorer. In these calculations, the total interaction energy was modeled as the sum of the electrostatic (E_{ele}), polarization (E_{pol}), dispersion (E_{dis}), and exchange-repulsion (E_{rep}) terms based on molecular wavefunctions calculated applying the crystal symmetry obtained from X-ray crystallographic results [38-40]. The electrostatic term corresponds to the classical electrostatic energy of interaction between monomer charge distributions, and repulsion term the exchange-repulsion energy, both of them are obtained from the antisymmetric product of the monomer spin orbitals. The polarization energy is estimated as a sum over atoms with terms of the kind $-1/2\alpha |F|^2$, with F being the electric field and α the isotropic atomic polarizabilities. The dispersion energy term is Grimme's D2 dispersion correction [38–40].

The supramolecular assembly presented in TAM (3a) and TACl (3b) systems is different as they crystallize in space groups $P_{2_1/n}$ and *P*-1, respectively. However, from a short distance perspective, equivalent pairs of N7–H71…N6^{i,ii} hydrogen bonds (symmetry codes (i): -1-x,2-y,1-z and (ii): 1-x,-y,1-z for TAM (3a) and TACl (3b), respectively) connect inversion-related molecules forming $R_2^2(8)$ centrosymmetric rings (Figs. 2a and 3a) (Table 2). It is



Fig. 1. Molecular structures and dihedral angles of (a) TAM and (b) TACI with anisotropic thermal vibration ellipsoids drawn at the 50% probability level. The hydrogen atoms are shown as spheres of arbitrary radius.



Fig. 2. (a). Inversion related molecules of TAM (3a) showing the N-H \cdots N hydrogen-bond interactions to form dimers. (b) Further connection of dimers through C-H \cdots O hydrogen-bond interactions. (c) and d) $\pi \cdots \pi$ stacking interactions between centroids of triazole and phenyl rings. The pairwise interaction energies were calculated based on references [38–40].

Table 2 Selected hydrogen-bond geometry (Å, $^{\rm o})$ for TAM (3a) and TACI (3b).

TAM (3a)				
D-H…A	D-H	Н…А	D…A	D-H…A
N7-H71…N6 ⁱ C16-H16…O9 ⁱⁱⁱ TACI (3b)	0.860(19) 0.96	2.10(2) 2.62	2.957(3) 3.567(3)	172(2) 169
N7-H71N6 ⁱⁱ C12-H12O9 ^v	0.859(19) 0.93	2.100(19) 2.68	2.955(2) 3.369(3)	174(2) 131

Symmetry codes: (i) –1-x, 2-y, 1-z; (ii) 1-x, -y, 1-z; (iii) –x+1/2, y+1/2, -z+3/2; (v) 1+x, y, z.

noteworthy that N···H distances are equivalents in both systems (2.10(2) Å and 2.100(19) Å for TAM (3a) and TACI (3b), respectively). This equivalence is observed in the pairwise interaction energies in these N7–H71···N6^{i,ii} hydrogen bonds, -66.2 kJ/mol, and -65.9 kJ/mol, respectively. The intermolecular N–H···N interactions

are dominated by electrostatic forces compared with other terms as shown in Table 3. The difference in the packing emerges in the mode in which the molecular dimers are connected. In TAM (3a), the methyl group substituted in the phenyl ring participates in the connection of the dimers through C16–H16-O9ⁱⁱⁱ (symmetry code (iii): -x+1/2, y+1/2, -z+3/2) hydrogen bonds with O···H distances of ~2.62 Å (Fig. 2b) (Table 2). The pairwise interaction energy for this contact is -27.6 kJ/mol but in this case, dispersion forces are the principal contributors to the total energy (Table 3). Important $\pi \cdots \pi^{iv}$ staking interactions are present to connect the centroids of triazole rings (3.8244(14) Å, symmetry code (iv): x,2-y,1-z) with total interaction energy of -20.8 kJ/mol with an obvious dominance of the dispersion energies (Fig. 2c). These interactions allow the molecules to have their molecular centers of mass relatively close, 9.30 Å, 7.48 Å and 6.63 Å for N-H-N, C-H-O and $\pi \cdots \pi$ (connecting the centroids of triazole rings), respectively (Table 3). However, $\pi \cdots \pi$ stacking of molecules along [100] direction involving the triazole and phenyl rings simultaneously al-



Fig. 3. (a). Inversion related molecules of TACI (3b) showing the N–H \cdots N hydrogen-bond interactions to form dimers. (b) Further connection of dimers through C–H \cdots O hydrogen-bond interactions. (c) $\pi \cdots \pi$ stacking interactions between centroids of phenyl rings. (d) C–Cl \cdots C halogen interactions along [–101] direction. The pairwise interaction energies were calculated based on references [38–40].

Table 3

Selected CrystalExplorer CE-B3LYP interaction energies (kJ/mol) for TAM (3a) and TACI (3b). N is the number of molecules with a molecular centroid-to-centroid distance R (A*). Electron density was calculated using B3LYP/6–31G(d,p) model energies. Symop is the symmetry operation.

Ν	Symop	R	E _{ele}	Epol	Edis	Erep	Etot
2	х, у, z	5.39	-6.5	-1.5	-42.7	21.7	-31.8
1	-x, -y, -z	9.30	-86.8	-19.9	-17.1	89.2	-66.2
1	-x, -y, -z	6.63	-0.5	-2.5	-31.5	14.6	-20.8
2	-x+1/2, y+1/2, -z+1/2	7.48	-11.6	-2.2	-30.5	20.7	-27.6
TACI (3b)							
Ν	Symop	R	E _{ele}	Epol	Edis	Erep	Etot
2	x, y, z	7.02	-4.4	-1.4	-21.2	11.4	-17.1
1	-x, -y, -z	10.19	-86.3	-19.4	-17.0	88.1	-65.9
1	-x, -y, -z	4.83	-7.9	-1.7	-59.7	34.3	-40.4
1	-x, -y, -z	7.63	-9.5	-2.9	-33.6	21.5	-28.2
1	-XV7	8.28	-5.9	-0.5	-21.4	16.7	-14.9

Note: scale factors used to determine E_{tot} : $E_{ele} = 1.057$; $E_{pol} = 0.740$; $E_{dis} = 0.871$; $E_{rep} = 0.618$.

low the molecules to have their centers of mass as close as possible in the crystal, 5.39 Å, with pairwise interaction energy of -31.8 kJ/mol (Fig. 2d). In this last case, the dispersion term dominates the contact (Table 3). The combination of these interactions and van der Waals forces act to build the three dimensions assemble.

In TACI (3b), C12–H12 \cdots O9^v (symmetry code (v): 1+x,y,z) hydrogen interactions connect the dimers along [100] direction (Fig. 3b and Table 2) with an pairwise interaction energy of -17.1 kJ/mol. In this contact, dispersion energy is the main term that contributes to the total energy (Table 3). These chains are further connected by two different $\pi \cdots \pi^{vi}$ (3.8607(12) Å and 3.9422(12) Å; symmetry code (vi): 2-x,-y,-z) interactions along [001] direction (Fig. 3c) (Table 2). As it can be observed, this $\pi \cdots \pi^{v_i}$ stacking occurs along [010] and involves molecules that have their molecular center of mass within a distance of 4.83 Å and 7.63 Å (3.8607(12) Å and 3.9422(12) Å between centroids, respectively) with pairwise interaction energies of -40.4 kJ/mol and -28.2 kJ/mol, in each case (Fig. 3c). Despite that this $\pi \cdots \pi^{vi}$ stacking allows the molecules to be closer compared with the N-H-N hydrogen interactions (10.19 Å between molecular centers of mass), in the last case, the high contribution from electrostatic forces makes the total interaction energy higher (Table 3). Interestingly, the molecular disposition in the crystal allows imagining the formation of weak C13–Cl16…C17^{vii} halogen interactions (symmetry code (vii): 3–x,-y,-z) with Cl…C distances of ~3.43 Å, between pairs of molecules related by inversion centers and running along [–101] (Fig. 3d). The pairwise interaction energy for this interaction was found to be –14.9 kJ/mol with the main contribution of dispersion forces (Table 3).

Computed energies between molecular pairs are represented using cylinders joining the centroids (molecular center of mass) of the molecules, with a radius proportional to the magnitude of the interaction managing a minimal cut-off of 15.0 kJ/mol. Figs. 4a and 4b show the energy framework diagrams for pairs of molecules for separate electrostatic (red) and dispersion (green) contributions to the total nearest-neighbor pairwise interaction energies (blue). In TAM (3a) and TACI (3b), the electrostatic energy is observed mainly in the N7–H71…N6^{i,ii} hydrogen bonds to connect inversion-related molecules. However, the three-dimensional assembly is due to dispersion forces having in both structures topologies with isotropic tendencies, certainly more structured in TACI (3b). This detailed structuration of the total interaction energy framework of TACI (3b) is reflected in the total structural energy, –95.3 kJ/mol and



Fig. 4. Energy framework diagrams for electrostatic (red) and dispersion (green) contributions to the total interaction energies (blue) in (a) TAM (3a) and (b) TACI (3b). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

CE-B3LYP structural energy components E for TAM (3a) and TACI (3b) (kJ/mol).

	E _{ele}	Epol	Edis	E _{rep}	Etot*
TAM (3a)	-62.1	-15.0	-86.1	91.1	-95.3
TACI (3b)	-64.5	-15.1	-118.6	108.7	-115.6

 * The total structural energy is the sum of scaled terms: $E_{structural}=1.057 Eele+0.740 Epol+0.871 E_{dis}+0.618$ $E_{rep},$ as described in [39].

-115.6 kJ/mol for TAM (3a) and TACI (3b), respectively, calculated based on the estimation of the interaction energies for selected molecular pairs in a coordination sphere of 10.0 Å around the asymmetric unit (Table 4). CE-B3LYP structural energies were then calculated by direct summation of total interaction energies over the asymmetric unit [41]. These values suggest a more stable crystal structure in TACI (3b) compared with TAM (3a) (Table 4).

Hydrogen bonds and other interactions enhance the stability of the supramolecular structure, and this behavior can be observed through Hirshfeld surface analysis, using the CrystalExplorer program [40–42], which allows the visualization of interactions within the crystalline structure, including N-H--N, C-H--O and C--Cl interactions. Assigning d_e and d_i as the external and internal distances of an atom to the Hirshfeld surface and normalizing these pairs of values to the van der Waals (Vdw) radii of the corresponding atoms results in the so-called d_{norm} surface. Contacts smaller than the sum of the Vdw radii of the two atoms result in a negative value highlighted on the surface in red. Contacts close to the limit of the Vdw radii are shown in white, and those contacts greater than the sum of the Vdw radii are highlighted on the surface in blue [43,44]. Hirshfeld surfaces (HFs) mapped over d_{norm} were calculated using TONTO [45], a Fortran-based object-oriented system for quantum chemistry and crystallography, by the B3LYP method using the 6-31G(d,p) basis set implemented in CrystalExplorer [40]. Fig. 5a shows that N7-H71...N6ⁱ and C16-H16...O9ⁱⁱⁱ hydrogen interactions are observed in the HFs mapped over dnorm for TAM (3a). However, a new contact no observed previously was detected. Weak nonbonding S...S interactions are contributing to the supramolecular assembly with a distance of 3.402 (1) Å (Fig. 5a).

Table 5

Participation percentages involving intermolecular contacts on the Hirshfeld surfaces.

	N…H	С…Н	0…H	C…Cl	Н…Н	S…H	Other
TAM (3a)	14.3	18.9	8.4	-	39.8	11.2	7.4
TACl (3b)	13.8	6.8	8.7	5.3	27.4	7.3	30.7

The N--H intermolecular contacts are similar for the two compounds; however, the C--Cl and Cl---H interactions contribute to the TACl (3b) compound with 18.7% of all intermolecular contacts on the Hirshfeld surface. C-H--- π/π ---H-C interactions become more frequent in the compound TAM (3a) (almost 3 times more) due to the involvement of the methyl group in this kind of interactions.

These sorts of intermolecular contacts are also observed in some organic conducting materials and proteins [46]. In TACI (3b), N7–H71…N6ⁱⁱ hydrogen bonds are observed while the remaining interactions present longer distances not highlighted as red spots in the d_{norm} maps (Fig. 5b).

The Hirshfeld surfaces mapped over d_{norm} indicates the locations of the strongest intermolecular contacts (red spots). *e.g.*, the N–H···N hydrogen bonds, which are the most important interactions in the crystal considering their intermolecular distances. When mapping d_e and d_i on this surface, these two values are associated; resulting in relations that are combined in intervals of 0.01 Å, providing the so-called fingerprint plots (Fig. 6). Table 5 summarizes the main intermolecular contacts and their percentage distributions on the Hirshfeld surface for the two compounds. An additional and relevant component of the TACl (3b) system that does not appear in Table 5 corresponds to the interaction Cl···H that comprises 12.3% of this surface.

A search in the CSD database version 5.41 (November 2019 with 2 updates May 2020) through the ConQuest software version 2020.1.1 for molecules with the same core, phenyl(1*H*-1,2,4-triazol-1-yl)methanone, gave as result no coincidence. However, recently, the crystallographic analysis of (5-amino-3-methylsulfanyl-1*H*-1,2,4-triazol-1-yl)(2-fluorophenyl)methanone was reported [17]. Considering that methanol was also used as a crystallization solvent, this compound crystallized in a Triclinic *P*-1 space group, with cell parameters *a* = 7.6599(9), *b* = 7.8079(8), *c* = 10.0140(12), α =94.487(9), β = 108.668 (11), and γ = 97.565 (9). In this case,



Fig. 5. (a). Packing diagram of d_{norm} surfaces displaying the N···H. O···H. and S···S pairwise interactions TAM (3a). (b) Packing diagram of d_{norm} surfaces displaying the N···H. and C···Cl pairwise interactions for TACl (3b).



Fig. 6. Two-dimensional fingerprint plots for (a) TAM (3a) and (b) TACI (3b) compounds and relative contributions of the atom pairs to the Hirshfeld surface.

the most related compound is TACI (3b), sharing similar interactions such as N-H····N hydrogen bonds to form inversion-related molecules, also observed in TAM (3a), C-H···O and $\pi \cdots \pi$ staking interactions involving the same groups. However, the structural difference appears due to the C-Cl···C halogen interactions along [-101] direction observed in TACI (3b) that change the packing.

3.3. Molecular comparison by crystallographic and theoretical studies

In order to study the electronic behavior of TAM (3a) and TACI (3b), geometric optimization was performed using Density Functional Theory (DFT) Becke's three-parameter hybrid function with the non-local correlation of Lee-Yang-Parr (B3LYP) method at 6–31G(d,p) basis set [29–31]. The conformational comparison between the optimized molecules and the crystal structure is shown in Fig. 7 and Table 6. The dihedral angles between the weighted least-squares mean planes that contain the phenyl and triazole rings are 64.82 °/65.32 ° and 31.94 °/32.59 ° for TAM (3a)/TACI (3b)



Fig. 7. Molecular structures of TAM (3a) and TACI (3b) obtained from (a) optimization by DFT and (b) X-ray crystal structure.

Optimized and experimental bond lengths (Å), bond angles (°) and torsion angles (°) of TAM (3a) and TACI (3b).

TAM (3a)				TACI (3b)	
Parameters ^a	Experimental (X-ray)	DFT/B3LYP 6-31G(d,p) ^b	Parameters ^a	Experimental (X-ray)	DFT/B3LYP 6-31G(d,p) ^b
Bond Lengths					
S(1) - C(2)	1.735(3)	1.765	Cl(16) - C(13)	1.741(2)	1.752
S(1) - C(17)	1.792(3)	1.827	S(1) - C(2)	1.7401(17)	1.764
O(9) - C(8)	1.223(3)	1.211	S(1) - C(17)	1.793(2)	1.828
N(3) - N(4)	1.406(2)	1.393	O(9) - C(8)	1.217(2)	1.210
N(3) - C(2)	1.309(3)	1.313	N(3) - C(2)	1.367(3)	1.313
N(4) - C(5)	1.385(3)	1.318	N(6) - C(5)	1.314(2)	1.317
N(4) - C(8)	1.398(3)	1.428	N(4) - N(3)	1.401(2)	1.393
N(6) - C(2)	1.370(3)	1.385	N(4) - C(5)	1.391(2)	1.387
N(6) - C(5)	1.321(3)	1.375	N(4) - C(8)	1.392(2)	1.424
N(7) - C(5)	1.322(3)	1.367	N(6) - C(2)	1.302(2)	1.376
C(8) > C(10)	1.481(3)	1.492	N(7) - C(5)	1.326(2)	1.367
C(10) - C(11)	1.398(3)	1.403	C(8) > C(10)	1.488(2)	1.495
C(10) - C(15)	1.392(3)	1.403	C(10) - C(15)	1.391(2)	1.402
C(11) - C(12)	1.380(3)	1.395	C(10) - C(11)	1.387(3)	1.394
C(12) - C(13)	1.387(3)	1.401	C(15) - C(14)	1.380(3)	1.390
C(13) - C(16)	1.507(3)	1.509	C(14) - C(13)	1.370(3)	1.397
C(13) - C(14)	1.386(3)	1.404	C(13) - C(12)	1.373(3)	1.395
C(14) - C(15)	1.377(3)	1.395	C(11) - C(12)	1.383(3)	1.394
Bond Angles					
C(2)-S(1)-C(17)	100.74(12)	100.19	C(2)-S(1)-C(17)	99.68(10)	100.24
S(1)-C(2)-N(3)	124.69(18)	123.17	S(1)-C(2)-N(6)	123.11(16)	120.38
N(4)-N(3)-C(2)	101.70(17)	102.00	N(6)-N(5)-C(7)	124.26(15)	118.97
N(4)-C(8)-C(10)	120.15(16)	116.60	N(5)-C(7)-C(9)	119.86(16)	116.66
C(5)-N(4)-C(8)	126.45(17)	131.05	C(4)-N(5)-C(7)	126.76(16)	131.11
C(2)-N(6)-C(5)	103.92(18)	102.72	C(2)-N(3)-C(4)	103.26(14)	102.80
Torsion Angles					
C(17)S(1)C(2)N(3)	9.3(2)	-117.61	C(17)S(1)C(2)N(6)	7.58(17)	-178.39
C(10)C(8)N(4)N(3)	1.1(3)	-152.71	C(9)C(7)N(5)N(6)	-2.9(2)	-152.82
N(6)C(5)N(4)C(8)	175.04(19)	167.83	N(3)C(4)N(5)C(7)	173.08(15)	167.62
N(4)C(8)C(10)C(11)	-31.5(3)	-149.82	N(5)C(7)C(9)C(15)	-30.3(2)	-149.60

^a The atom numbering scheme of the molecular structure is given in Fig. 1.

^b Deviation from experimental and calculated data. a) Bond lengths. TAM: y = 1.0412x - 0.0466 (R² = 0.9697), TACI: y = 1.0208x - 0.0163 (R² = 0.9756). b) Bond angles. TAM: y = 1.0451x - 5.4095 (R² = 0.957), TACI: y = 0.9545x + 4.1625 (R² = 0.9168).



Fig. 8. Molecular electrostatic potential mapped for a) TAM (3a) and b) TACl (3b).

molecules, optimized and crystal structure, respectively. This result establishes a clear conformational difference between them.

3.4. Molecular electrostatic potential mapped (MEP)

The molecular electrostatic potential mapped (MEP) is a stratagem of electrostatic potential mapping onto the iso-electron density surface simultaneously displays molecular shape, size, and electrostatic potential values and it has been plotted for molecule under investigation using B3LYP method. The color scheme for the MEP surface is red, electron rich; blue, electron deficient; light blue, slightly electron deficient region; yellow, slightly electron rich region, respectively [47]. The MEP calculations were performed to find the charge distribution on the surface of the 1,2,4-triazole-based amides TAM (3a) and TACI (3b), as well as to determine the regions of that surface with higher or lower potential, which may assure an anchoring with other molecules in synthesis con-

ditions. Regions with negative potentials have a high probability of performing nucleophilic attacks or undergoing protonation reactions. Theoretical calculations of MEP for 1-(2-fluorophenyl)-3methylsulfanyl-5-amino-1,2,4-triazole (TAF) indicates that N2 atom contains a minimum potential value of -38.898 kcal/mol [17]. Theoretical calculations reported under the same reaction conditions with the NH-1,2,4-triazole 1, confirmed a prototropic behavior favored by its 1*H*-form tautomer with higher energetic stability [17]. MEP studies performed on the most stable tautomer showed consistent results with a maximum potential value over the N4-H region, which would confirm the formation of covalent bonds in this region in case of an acylation reaction with the presence of an acylating agent [17]. The acylation reaction between NH-1,2,4-triazole 1 and aroyl chlorides in the presence of triethylamine showed high chemo- and regioselectivity towards the formation of the 1,2,4-triazole-based amides TAM (3a) and TACl (3b), whose MEP values appear in Fig. 8. The MEP total density of the molecules



Fig. 9. HOMO-LUMO transitions obtained from the calculated spectra (isovalue = 0.02) of TAM (3a) from (a) crystal structure (b) optimized from DFT, and TACI (3b) from (c) optimized from DFT (d) crystal structure.

(3a) and (3b) clearly shows the presence of more electron density characterized by red color around the N2 atom of the 1,2,4triazole with minimum potential values of -52.553 kcal/mol and -49.137 kcal/mol, respectively. The predominance of green regions in the MEP surfaces corresponds to a potential halfway between the two extremes red and dark blue color. The results suggest that 1,2,4-triazole-based amides were found to be useful to both bond metallically and interact intermolecularly.

3.5. Frontier orbitals and global reactivity descriptors

The energy levels of the HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) for TAM (3a) and TACI (3b) were computed using DFT for the optimized molecules, and the B3LYP method using the 6-31 G (d,p) basis set implemented in CrystalExplorer using TONTO, a Fortran-based object-oriented system for quantum chemistry and crystallography. Fig. 9 shows the results from both calculations. It is possible to conclude that DFT calculations from the molecules optimized and the crystal structures are comparable between them. The measured maximum wavelengths as well as the computed data are summarized in Table S3 (see Supporting Information). The LUMO as an electron acceptor represents the ability to obtain an electron while HOMO represents the ability to donate an electron. It is important to mention that electron-withdrawing groups (i.e. chlorine and bromine) would decrease the energy of the LUMO, while electrondonating groups (i.e. methyl, methoxy, and hydroxyl) would increase its energy. Indeed, the energy gap between the HOMO and LUMO molecular orbitals is an important parameter in determining molecular electrical transport properties and the chemical reactivity of the molecule. As shown in Fig. 9, the HOMO-LUMO energy gap values are 4.20 eV and 4.03 eV for TAM (3a) and TACl (3b), respectively. As expected, the slightly lower value in the energy gap of TACl (3b) explains the eventual charge transfer interactions taking place within the molecule because of the presence of a chlorine atom on the benzene ring which may decrease the energy of the LUMO.

The calculated Ionization Potential (IP), Electron Affinity (EA), Electrophilicity Index (ω), Chemical Potential (μ), Electronegativity (χ), Hardness (η), Electrodonating Power (ω^{-}), Electroaccepting Power (ω^{+}), and Net Electrophilicity ($\Delta \omega^{\pm}$) for TAM (3a) and TACl (3b) are presented in Table 7. In simple molecular orbital theory approaches, the HOMO energy (ε_{HOMO}) is correlated to the ionization potential (IP) by Koopmann's theorem and the LUMO energy (ε_{LUMO}) has been used to calculate the electron affinity (EA) [46]. The average value of the HOMO and LUMO energ

Table 7
HOMO and LUMO orbital energies (in eV) and global rea
tivity descriptors (in eV) for TAM (3a) and TACI (3b).

Parameters	TAM (3a)	TACl (3b)
HOMO energy	-6.04	-6.08
LUMO energy	-1.84	-2.05
HOMO-LUMO energy gap	4.20	4.03
Ionization Potential (IP)	6.04	6.08
Electron Affinity (EA)	1.84	2.05
Electrophilicity Index (ω)	1.84	2.05
Chemical Potential (μ)	3.94	4.07
Electronegativity (χ)	3.94	4.07
Hardness (η)	4.20	4.03
Electrodonating power (ω^{-})	5.94	6.40
Electroaccepting power (ω^+)	2.00	2.33
Net electrophilicity ($\Delta \omega^{\pm}$)	7.94	8.73

gies is related to the electronegativity (χ), as $\chi = (IP + EA)/2$ [49]. The HOMO-LUMO gap is related to the hardness (η) [48,49]. The electrophilicity is a descriptor of reactivity that allows the quantitative classification of the global electrophilic nature of a molecule within a relative scale. Parr *et al.* [50,51] suggested the term electrophilicity index (ω), as $\omega = \mu^2/2\eta$ where μ is the chemical potential taking the average value $\mu = -$ (IP + EA)/2 [52–54]. In addition, Gázquez *et al.* represented the local electrodonating power $\omega^- = [(3IP + EA)^2/16(IP - EA)]$, electroaccepting power $\omega^+ = [(IP + 3EA)^2/16(IP - EA)]$, and net electrophilicity $\Delta \omega^{\pm} = \omega^+ + \omega^-$ [52–54].

A small HOMO–LUMO gap means small excitation energies to the manifold of excited states. Therefore, soft molecules, with a small gap, will have their electron density changed more easily than a hard molecule. In terms of chemical reactivity, we can conclude that soft molecule TACI (3b) would be more reactive than hard molecule TAM (3a) due to its smaller HOMO–LUMO gap (4.03 eV). It is important to mention that the presence of a chlorine atom on the benzene ring would decrease the energy of the LUMO orbital. Moreover, when IP is small and EA is large and positive, the molecule should be soft. Once again, these global reactivity descriptors confirm that TACI ($\eta = 4.03$) is softer than TAM ($\eta = 4.20$).

The electrophilicity (ω) index encompasses the balance between the tendency of an electrophile to acquire electron density and the resistance of a molecule to exchange electron density. Interestingly, Domingo *et al.* [55] established an electrophilicity (ω) scale for the classification of organic molecules as strong electrophiles with $\omega > 1.5$ eV, moderate electrophiles

Most	relevant	assignments	of the	calculated	and e	experimental	vibrational	frequencies	in terms	of PED	analysis.

TAM (3a)						TACl (3b)	
Assignment	Experimental (cm ⁻¹)	Scaled DF	Γ (B3LYP) Calc.(cm ⁻¹) PED%	Assignment	Experimental (cm ⁻¹)	Scaled DF	T (B3LYP) Calc. (cm ⁻¹) PED%
vas N-H	3419.79	3561.71	100	ν _{as} N-H	3431.24	3567.51	100
vs N-H	3278.99	3447.06	100	vs N-H	3275.03	3453.12	100
$\nu C = N_{triazole}$	1496.76	1475.05	75	$\nu C = N_{triazole}$	1498.62	1474.14	69
	1381.03	1368.08	46		1377.05	1365.70	_
v_{as} CH ₃	-	3012.23	93	v_{as} CH ₃	-	-	-
	-	2983.52	93		-	-	-
$\nu_s CH_3$	-	2924.25	95	$\nu_s CH_3$	-	-	-
v_{as} S-CH ₃	-	3054.28	99	v_{as} S-CH ₃	3051.26	3055.01	99
	-	3046.33	94		2993.40	3047.00	94
v_s S-CH ₃	-	2955.54	95	v_s S-CH ₃	2933.70	2956.08	95
ν C=0	1680.00	1732.19	90	ν C=0	1674.21	1732.01	90

v. Stretching; δ . Bending; ω . Wagging; τ . Twisting; s. Symmetric; as. Asymmetric.



Fig. 10. Superposition of observed and DFT (B3LYP)/6-31 G (d,p) calculated FT-IR spectra of a) TAM (3a), and b) TACI (3b).

with 0.8 < ω < 1.5 eV, and marginal electrophiles with ω < 0.8 eV. As shown in Table 7, *N*-aroyl-1,2,4-triazoles (3) considered in this study can be regarded as strong electrophiles, which is in agreement with the net electrophilicity index ($\Delta \omega^{\pm}$). As expected from the molecular structure of TAM (3a) and TACl (3b), their electron-donating ability (ω^{-}) is more important than their electron-accepting character (ω^{+}).

3.6. Vibrational analysis

The detailed vibrational assignments of fundamental modes in terms of PED% are reported in Tables S1 and S2 (see Supporting Information), but Table 8 lists the most relevant theoretical and experimental wavenumbers. For visual comparison, a superposition of observed and simulated FT-IR spectra is presented in Fig. 10. As

it is well known, vibrational frequencies from DFT calculations are often overestimated and are commonly scaled by empirical factors. The main reasons because of this are necessary are: first, the theoretical model does not consider the vibrational anharmonicity of the real system, and second, the incomplete treatment of electron correlation. A scaling factor of 0.9613 was used in this study to fit the calculated frequencies to the experimental ones [56].

3.6.1. N–H stretching

Primary amines present two medium to weak intensity bands in the region around 3520–3420 cm⁻¹ and 3420–3340 cm⁻¹ due to the asymmetric and symmetric N–H stretching vibrations, respectively [57]. In the experimental IR spectrum, absorption bands at 3419.79 cm⁻¹ (ν_{as} N–H) and 3278.99 cm⁻¹ (ν_{s} N–H) were observed for TAM (3a), while absorption bands at 3431.24 cm⁻¹ (ν_{as} N–H) and 3275.03 cm⁻¹ (ν_{s} N–H) were observed for TACI (3b) (Table 8). Moreover, the calculated scaled vibrations were 3561.71 cm⁻¹ and 3447.06 cm⁻¹ for TAM (3a), and 3567.51 cm⁻¹ and 3453.12 cm⁻¹ for TACI (3b), respectively. The downshifting of the experimental values related to the calculated ones responds to the intermolecular interactions in the solid-state involving N–H…O hydrogen bonds; interactions that are not observed in the optimized molecules by DFT.

The $-NH_2$ bending vibrations appear in the region around 1700–1600 cm⁻¹ for scissoring, and 1150–900 cm⁻¹ for rocking. Theoretical studies show that computed $-NH_2$ bending vibrations appear at 1604.12 cm⁻¹, 1524.29 cm⁻¹, and 1061.40 cm⁻¹ for TAM (3a), and 1605.15 cm⁻¹, 1525.23 cm⁻¹, and 1058.74 cm⁻¹ for TACI (3b); nonetheless, all bands appear as mixed vibrations. Experimental frequencies were observed at 1639.49 cm⁻¹, 1606.70 cm⁻¹, and 1089.78 cm⁻¹ for TAM (3a), and 1637.51 cm⁻¹, 1587.34 cm⁻¹, and 1087.76 cm⁻¹ for TACI (3b), respectively. It is important to note that calculated and experimental values are in good agreement.

3.6.2. C=0 stretching

Carbonyl group of the amide functionality shows a very strong band due to the C=O stretching vibration. Albeit the carbonyl absorption band of tertiary amides often appears in the region 1680– 1630 cm⁻¹ [58], it probably shifted to higher frequencies because the nitrogen atom belongs to triazole ring [59]. As depicted in Table 8, computed scaled frequencies appeared at 1732.19 cm⁻¹ for TAM (3a), and 1732.01 cm⁻¹ for the TACl (3b), which is according to previously reported data [60]. From experimental results, the C=O stretching vibration was assigned at 1680.00 cm⁻¹ and 1674.21 cm⁻¹ for TAM (3a) and TACl (3b), respectively. Once again, the difference between experimental and computed values arises from the intermolecular interactions previously mentioned.

3.6.3. C-H vibrations

The presence of weak intensity bands in the region above 3000 cm^{-1} due to C–H stretching vibrations is a remarkable feature of the presence of an aromatic ring [61]. As shown in Table 8, the calculated frequencies appeared at 3094.12 cm⁻¹, 3078.65 cm⁻¹, 3062.11 cm⁻¹, and 3060.50 cm⁻¹ for TAM (3a), and at 3104.05 cm⁻¹, 3100.45 cm⁻¹, 3091.78 cm⁻¹, and 3078.35 cm⁻¹ for TACl (3b), which is in good agreement with the literature data.

Methyl group bonded to the aromatic ring absorbs in the range of 3010–2905 cm^{-1} and 2945–2845 cm^{-1} due to asymmetric and symmetric C-H stretching vibrations, respectively [62]. It is important to note that compound TAM (3a) has one -CH₃ group bonded to the phenyl ring, and one -SCH₃ bonded to the triazole ring, while the compound TACl (3b) only has the -SCH₃ group. Gratifyingly, the computed C-H(CH₃) scaled asymmetric stretching vibrations were observed at 3012.23 cm⁻¹ and 2983.52 cm⁻¹, while the C-H(CH₃) symmetric stretching vibration was observed at 2924.25 cm⁻¹ for the compound TAM (3a). As expected, these vibrations are absent for the compound TACl (3b). On the other hand, the methyl group directly bonded to electron-withdrawing heteroatoms absorbs at slightly higher energies than these previously discussed. For example, asymmetric and symmetric (S-)C-H stretching vibrations are observed in the region 3040–2980 cm⁻¹ and 3030-2935 cm⁻¹, respectively [59]. The computed (S-)C-H scaled asymmetric stretching vibrations values were 3054.28 cm⁻¹ and 3046.33 $\rm cm^{-1}$ for TAM (3a), while at 3055.01 $\rm cm^{-1}$ and 3047.00 cm⁻¹ for TACl (3b). Ultimately, the computed (S-)C-H scaled symmetric stretching vibrations values were 2955.54 cm⁻¹ and 2956.08 cm⁻¹ for compounds TAM (3a) and TACl (3b), respectively.

The experimental C–H stretching vibrations mainly appear at 3174.83 cm⁻¹, 3088.03 cm⁻¹, 2997.38 cm⁻¹, and 2929.87 cm⁻¹ for the compound TAM (3a), and at 3172.85 cm⁻¹, 3086.07 cm⁻¹,

2995.33 cm⁻¹, and 2933.70 cm⁻¹ for the compound TACl (3b). For each case, we assigned the last two bands to aliphatic C–H vibrations. Unfortunately, we could not determine if the aliphatic vibrations observed for TAM (3a) corresponding to $-CH_3$ or $-SCH_3$ stretching vibrations. Despite that, our results are in good agreement with the calculated values and also the literature data.

3.6.4. C=N and C-N vibrations

The interpretation of vibrational spectra of triazoles in the fingerprint region is difficult due to the mixing of several bands [62,63], but by making use of the GaussView graphical interface was possible to identify C=N stretching assignments. For the TAM (3a), the most relevant computed scaled frequencies attributed to C=N stretching vibrations were 1475.05 cm⁻¹ and 1368.08 cm⁻¹, while for the TACl (3b) the computed scaled band at 1474.14 cm⁻¹ is due to C-N stretching vibration and 1365.70 cm⁻¹ arises from the C=N stretching vibration. Mentioned vibrations were assigned at 1496.76 cm⁻¹ and 1379.10 cm⁻¹ for TAM (3a), while 1498.62 cm⁻¹ and 1377.05 cm⁻¹ for TACl (3b).

3.6.5. C-Cl vibrations

Chlorine compounds absorb strongly in the region 760–395 cm⁻¹ due to C–Cl stretching vibrations [64]. However, the PED% assignment of the IR spectrum of TACl (3b) indicated the absence of a pure C–Cl stretching vibration band. The calculated band at 452.91 cm⁻¹ represents a mixed-mode involving wagging of ClCCC moiety, stretching of C–N bond, and torsion around the carbon skeleton of the benzene ring. Moreover, the calculated band at 436.01 cm⁻¹ also involves a mixed-mode with a minor contribution of the bending vibration of the CCCl group (see Supporting Information).

4. Conclusions

In summary, we have synthesized functionalized N-aroyl-1,2,4triazoles (3a) and (3b) in excellent yields via a high chemo- and regioselective acylation reaction from NH-1,2,4-triazole and aroyl chlorides in the presence of triethylamine in air. This straightforward and efficient method is distinguished by its reduced reaction time, high yielding, and operational simplicity, allowing a substantial improvement over other previously described methods for the synthesis of N-aroyl-1,2,4-triazole analogs. The crystal structures of TAM (3a) and TACl (3b) are characterized by the formation of molecular dimers which are further connected by different sorts of intermolecular interactions inducing crystallization in the $P2_1/n$ and P-1 space groups, respectively. Hirshfeld surface maps over d_{norm} allowed to identify weak nonbonding S···S interactions contributing to the supramolecular assembly. The interaction of inversion-related molecules (dimers) by N-H-N hydrogen bonds constitutes the stronger force acting between pairs of molecules. Despite that N-H--N interactions are mainly represented by electrostatic energies, the three-dimensional crystal structures are dominated by dispersion forces. The MEP total density of TAM (3a) and TACl (3b) clearly shows the presence of more electron density around the N2 atom of the 1,2,4-triazole ring with minimum potential values of -52.553 kcal/mol and -49.137 kcal/mol, respectively. The calculated frontier molecular orbital energies and global reactivity descriptors showed that soft molecule TACl is more reactive than hard molecule TAM due to its smaller HOMO-LUMO gap (4.03 eV); thus, the presence of a chlorine atom on benzene ring would decrease the energy of the LUMO orbital. Vibration frequency assignments of triazole-based amides 3 were performed using energy distribution analysis (PED) with VEDA4 software. A statistical study showed similar results with the use of both basis set 6-31G(d,p) and 6-311+G(d,p). Thus, fundamental vibrational frequencies and intensity of vibrational bands

were evaluated using density functional theory (DFT) with the B3LYP/6–31G(d,p) method and basis set, yielding fairly good agreement between observed and calculated frequencies. Ultimately, exocyclic amine and thiomethyl moieties into *N*-aroyl-1,2,4-triazoles 3 would be susceptible to functionalization reactions for obtaining biologically active 1,2,4-triazole derivatives of great interest in both drug discovery and pharmaceutical industry.

Crystallographic data

Crystallographic data for the structural analysis have been deposited in the Cambridge Crystallographic Data Center, CCDC, with deposition numbers 2,011,149–2,011,150. A copy of this information may be obtained free of charge from CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: +44–1223–336,033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

Author contributions

The manuscript was written through the contributions of all authors. All authors have approved the final version of the manuscript.

Notes

The authors declare no competing financial interest.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

CRediT authorship contribution statement

Rodolfo Moreno-Fuquen: Writing - review & editing, Investigation, Data curation. **María Mercedes Hincapié-Otero:** Data curation, Investigation. **Diana Becerra:** Writing - original draft, Investigation. **Juan-Carlos Castillo:** Writing - original draft, Investigation, Conceptualization. **Jaime Portilla:** Writing - review & editing, Resources, Investigation. **Mario A. Macías:** Writing - original draft, Data curation, Investigation.

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Supplementary material

Supplementary material associated with this article can be found, in the online version, at 10.1016/j.molstruc.2020.129317.

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