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AN EFFICIENT TWO-STEP SYNTHESIS OF NOVEL SUBSTITUTED PYRAZOLO[1,5-a]-[1,3,5]-TRIAZINES AND PYRAZOLO[1,5-a]-[1,3,5] TRIAZINONES

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ABSTRACT
The synthesis of a series of pyrazolotriazine derivatives is described in two steps. The reaction of hydrazine with substituted thioamides leads to the formation of 3,5-diaminopyrazoles. The latter reacts with the N-acyl imidates and the N-ethoxy imidate yielding the corresponding substituted pyrazolotriazines and pyrazolotriazinones. The structure of all these compounds has been confirmed by IR, ^{1}HNMR, ^{13}CNMR and elemental analysis.

KEYWORDS
Thioamides; hydrazine; 3,5-diaminopyrazole; *N*-acyl imidate; N-ethoxy imidate; pyrazolotriazine, pyrazolotriazinone.

INTRODUCTION
It is well known that nitriles are widely used as intermediates for a large number of heterocyclic compounds. Aminopyrazole compounds can be readily obtained by the reaction of nitrile derivatives with hydrazine hydrate[1-4].
Besides, several pyrazole ring systems are associated with antifungal, antitubercular, antibacterial, antiviral anticancer and antioxidant activities[5-7] , as well as the biological activities of pyrazolotriazine ring systems are well documented[8-10].
Derivatives of the ring system pyrazolo[1,5-a]-[1,3,5]-triazine as significantly interesting as purine analogues.[11,12] Additionally, these compounds are active agents to inhibit bronchial inflammation (**1, Fig. 1**)[11d] and are useful in the treatment and prevention of central nervous system disorders,[11e] such as psychosis, schizophrenia, depressions, memory disorders, Parkinson's disease, Alzheimer's disease and Huntington's chorea (**2, Fig. 1**).
The most common strategy for preparing pyrazolo[1,5-a]-[1,3,5]-triazines is the reaction between 3,5-diaminopyrazoles and an appropriate biselectrophilic reagent.[11c,12]
The N-acyl imidates and the N-ethoxy imidate are efficient bielectrophiles that have been widely used in the synthesis of many heterocyclic compounds, such as monocyclic 1,3,5-triazines.[13,14]As for as we know, their use has not been reported for the preparation of pyrazolo[1,5-a]-[1,3,5]-triazines. We describe here the interaction of N-acyl imidates (**6a,b)** or N-ethoxy imidate **8** with 3,5-diaminopyrazoles (**5a-d)** (**Scheme 1**) as an efficient and versatile method to obtain novel pyrazolo[1,5-a]-[1,3,5]-triazines (**7a-d)** and pyrazolo[1,5-

a][1,3,5] triazinones (**9a,b)**, interesting compounds as regards to their potential biological activity.[11,12,15]

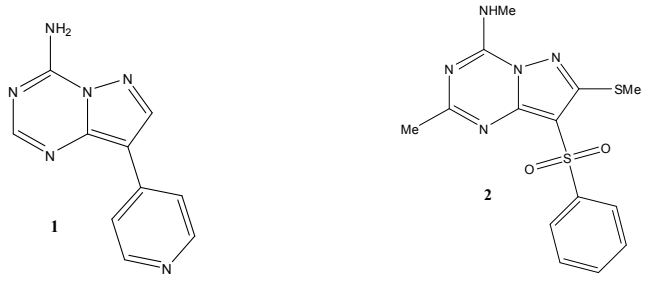
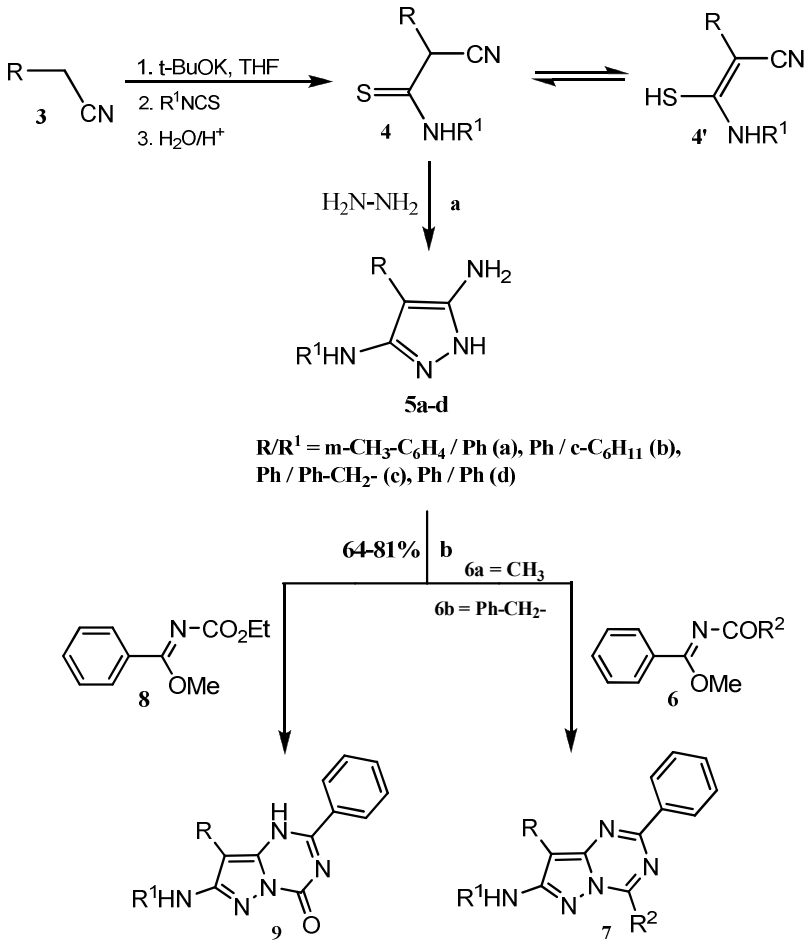


Figure 1

RESULTS AND DISCUSSION

The synthetic strategies adopted to obtain the corresponding pyrazolotriazines (**7a-d)** and pyrazolotriazinones (**9a,b**) are depicted in **Scheme 1**. The starting material 3,5-diaminopyrazole (**5)** was prepared by combining thioamide (**4)** with hydrazine hydrate in ethanol.[16]

We have devided an efficient one-step procedure for the synthesis of new pyrazolo[1,5-a]-[1,3,5] triazines (**7a-d)** and pyrazolo[1,5-a][1,3,5] triazinones (**9a,b**) from 3,5-diaminopyrazole (**5)** and N-acyl imidates (**6a,b)** or the N-ethoxy imidate **8**. Thus, equimolar amounts of (**5a-d)** and (**6a,b)** or **8** were refluxed in absolute ethanol (EtOH) under the influence of glacial acetic acid to give compounds (**7a-d)** or (**9a,b**) for an extended reaction time of 48h and with good yields. Spectral characteristics are also discussed (**Table 1**).



Scheme 1: Synthesis of pyrazolo[1,5-a]-[1,3,5] triazines and pyrazolo[1,5-a][1,3,5] triazinones

Reagents and conditions: (a) Ethanol, RT, 48h (b) Absolute Ethanol, acetic acid glacial, reflux, 48h

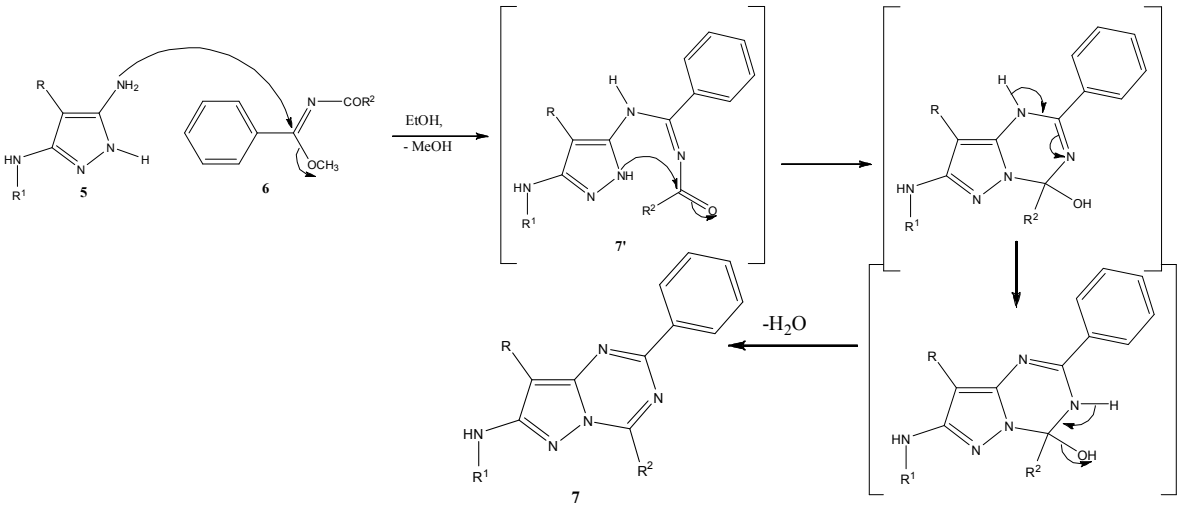
Table 1: Yields of compounds synthesized

	R	R^1	R^2	Yield, (%)
7a	m-CH_3-C_6H_4	Ph	CH_3	64
7b	Ph	c-C_6H_{11}	CH_3	76
7c	Ph	Ph-CH_2-	Ph-CH_2-	77
7d	Ph	Ph	Ph-CH_2-	81
9a	m-CH_3-C_6H_4	Ph		65
9b	Ph	c-C_6H_{11}		67

The structures of all new compounds were established by spectroscopic methods (IR, NMR ^{1}H and ^{13}C). The NMR spectra of the compounds conformed with their structures. Furthermore, the IR spectra of compounds **7** or **9** displayed an absorption at 1544 cm^{-1} corresponding to C=N and C=C stretching vibrations and at 3211-3278 cm^{-1} for the NH

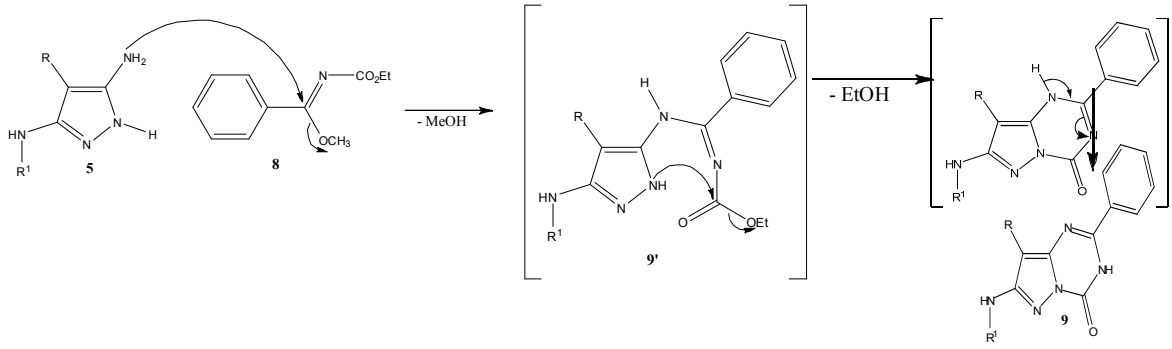
group and no NH_2 absorption at 3300-3600 cm^{-1} was observed. The reaction of compounds (**5a-d**) with N-acyl imidate in refluxing ethanol provided the products (**7a-d**). Moreover, the reaction of compounds (**5a,b**) with appropriate N-ethoxy imidate under similar reaction conditions yielded the products (**9a,b**). The ^1H NMR spectrum of these compounds revealed singlet signals with δ values between 2.65 ppm and 2.72 ppm corresponding to the CH_3 protons, a signal at 4.58ppm attributed to ($-CH_2$-Ph), whereas the singlet signals with δ values from 6.11 ppm to 6.78 ppm which can be assigned to (NH-CO) in addition to other signals attributable to the aromatic compounds. The ^{13}C NMR data also confirmed this result, showing signals at δ values of 157.77-179.10 and 167.73-178.85 ppm assigned to respective carbons of C=N and C=O.

Hence, the formation of **(7a-d) (Scheme 2)** is assumed to proceed through an initial addition then elimination: first, the C=N double bond of compound **6** undergoes an addition from exocyclic nitrogen at pyrazole **5**, which after subsequent methanol elimination, affords the adduct **7'**, that after further intramolecular cyclocondensation between endocyclic NH and carbonyl group followed by water removal, leads to pyrazolotriazine **7**.



Scheme 2 Mechanism reaction

In similar manner, the aminopyrazole **5** reacted to the N-ethoxy imidate **8** in absolute ethanol to afford the corresponding product **9'.** Cyclizations of the resulted hydrazone **9'** under acidic condition gave the desired pyrazolotriazinone **9** (**Scheme 3**).



Scheme 3 Mechanism reaction

CONCLUSION

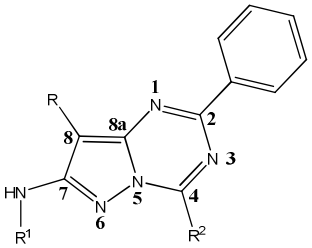
We reported a simple and practical method for the preparation of novel pyrazolo[1,5-a]-[1,3,5]-triazines in a short reaction time and with good yields, under mild conditions.
Our findings are an important contribution to confirm the selectivity and the mechanism of this kind of reactions.

EXPERIMENTAL SECTION

The melting point was determined by Bûchi. Infrared spectra were recorded by using Shimadzu FTIR 8400S. ^{1}H, ^{13}C NMR spectra were recorded at 300, 75 MHz respectively on a Bruker AC-300 with TMS as internal reference (for ^{1}H and ^{13}C). Materials: thin-layer chromatography (TLC): TLC plates (Merck, silica gel 60 F254 0.2 mm 200×200 nm); substances were detected using UV light at 254 nm. CHN elementary were performed at the INRAP (National Institute of Physico-Chemical Analysis (INRAP) Bio-technopole Sidi Thabet, Tunisia) Perkin Elmer Model: Analyzer 2400 series II CHN.

General procedure for the preparation of pyrazolo[1,5-a][1,3,5] triazine and pyrazolo[1,5-a][1,3,5] triazinone

A mixture of aminopyrazole **1** (1 mmol), N-acyl imidates **2** or N-ethoxy imidate **3** (2 mmol), and drops of acetic acid glacial (0.5 mL) were heated under reflux in absolute ethanol (10mL) for 48 h, the solvent was removed under reduced pressure, the residue was treated with petroleum ether. The formed precipitate was filtrated and the residue obtained was recrystallized with ether and petroleum ether.



4-methyl-N,2-diphenyl-8-m-tolylpyrazolo[1,5-a][1,3,5]triazin-7-amine (7a)

Orange solid; mp= 229°C; ^{1}H NMR ($CDCl_3$, δ_H ppm): 2.18 (s, 3H, m-CH_3-C_6H_4); 2.41 (s, 3H, CH_3-C_6H_4); 7.46 (1H, NH) 6.65-8.69 (m, H_{arom}); IR spectrum ($CHCl_3$, ν cm^{-1}): (C=C)= 1623.56; (NH) = 3092.47. ^{13}C NMR ($CDCl_3$, δ_C ppm): 19.48 (s, 3H, CH_3-C_6H_4); 21.57 (s, 3H, CH_3-C_6H_4); 170.7 (C_2); 166.1064 (C_4); 137.64 (C_7); 94.47 (C_8); 142.42 (C_{8a}); 114.19-137.64 (C_6H_5). Anal. Calc. for $C_{25}H_{21}N_5$ (391g.mol^{-1}): C, 76.72; H, 5.37; N, 17.90; found C, 76.70; H, 5.40; N, 17.89 %.

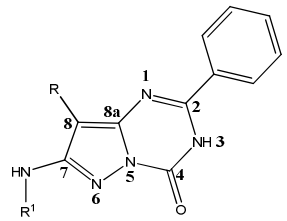
N-cyclohexyl-4-methyl-2,8-diphenylpyrazolo[1,5-a][1,3,5]triazin-7-amine (7b)

Yellow solid; mp= 201°C; ^{1}H NMR ($CDCl_3$, δ_H ppm): 1.06-1.98 (m, 11H, $H_{cyclohexyl}$); 4.21-4.26 (m, 1H, H_{ipso}); 7.45 (1H, HN); 7.14-8.24 (m, H_{arom}) ; IR spectrum ($CHCl_3$, ν cm^{-1}): (C=C)= 1620.16; (NH) = 3102.26. ^{13}C NMR ($CDCl_3$, δ_C ppm): 24.7 (s, 3H, CH_3); 52.84 (N-C_{ipso}); 24.91-33.91 (c-C_6H_{11}); 179.10 (C2); 128.63-132.50 (C_6H_5). Anal. Calc. for $C_{24}H_{25}N_5$ (383g.mol^{-1}): C, 75.19; H, 6.52; N, 18.27; found C, 75.24; H, 6.50; N, 18.12 %.

N,4-dibenzyl-2,8-diphenylpyrazolo[1,5-a][1,3,5]triazin-7-amine (7c)

Yellow solid; mp= 175°C; ^{1}H NMR ($CDCl_3$, δ_H ppm): 4.54 (s, 2H, CH_2-Ph); 4.73 (d, J= 5.8 Hz, 2H, CH_2-NH); 7.38 (1H, NH); 7.25-8.50 (m, H_{arom}); IR spectrum ($CHCl_3$, ν cm^{-1}): (C=C) = 1588; (NH) = 3158. ^{13}C NMR ($CDCl_3$, δ_C ppm): 38.34 (=C-CH_2-Ph); 41.76 (NH-CH2-Ph); 156.15 (C_2); 157.77 (C_4); 155.10 (C_7); 97.64 (C_8); 118.05 (C_{8a}); 120.88-145.85 (C_6H_5). Anal. Calc. for $C_{32}H_{25}N_5$ (479g.mol^{-1}): C, 80.16; H, 5.21; N, 14.61; found C, 80.14; H, 5.26; N, 14.59 %.

4-benzyl-N,2,8-triphenylpyrazolo[1,5-a][1,3,5]triazin-7-amine (7d)
Yellow solid; mp= 188 °C; ^{1}H NMR ($CDCl_3$, δ_H ppm): 4.58(s, 2H, CH_2); 7.96 (1H, NH) 6.94-8.45 (m, H_{arom}); IR spectrum ($CHCl_3$, ν cm^{-1}): (C=C)= 1598.2; (NH) = 3126.35. ^{13}C NMR ($CDCl_3$, δ_C ppm): 38.34 (CH_2-Ph); 43.18 (CH_2-NH); 173.79 (C_2); 169.76 (C_4); 131.89 (C_7); 95.83 (C_8); 146.80 (C_{8a}); 125.94-159.05 (C_6H_5). Anal. Calc. for $C_{31}H_{23}N_5$ (465g.mol^{-1}): C, 80.00; H, 4.94; N, 15.05; found C, 80.01; H, 4.89; N, 15.04 %.



2-phenyl-7-(phenylamino)-8-m-tolylpyrazolo[1,5-a][1,3,5]triazin-4(3H)-one (9a)
Orange solid; mp= 192°C; ^{1}H NMR δ_H (ppm): 2.20 (s, 3H, H_3C); 6.50 (1H, HN-Ph); 8.75 (d, J= 7.7, 1.9 Hz, 1H, NH-CO); 6.66-7.95 (m, H_{arom}); IR spectrum ($CHCl_3$, ν cm^{-1}): (C=C) = 1608; NH = 3112.26. ^{13}C NMR δ_C (ppm): 21.50 (H_3C); 167.97 (C_2); 146.97 (C_4); 144.40 (C_7); 95.49 (C_8); 145.85 (C_{8a}); 116.01-146.97 (C_6H_5). Anal. Calc. for $C_{24}H_{19}N_5$ (377g.mol^{-1}): C, 76.39; H, 5.03; N, 18.56; found C, 76.28; H, 5.12; N, 18.54 %.

7-(cyclohexylamino)-2,8-diphenylpyrazolo[1,5-a][1,3,5]triazin-4(3H)-one (9b)
Yellow solid; mp= 218°C; ^{1}H NMR δ_H (ppm): 1.24-1.91 (m, 11H, $H_{cyclohexyl}$); 4.21-4.31 (m, 1H, H_{ipso}); 6.12 (1H, HN-C_6H_{11}); 8.69 (d, J=7.8Hz, 1H, NH-CO); 7.22-7.97 (m, H_{arom}); IR spectrum ($CHCl_3$, ν cm-1): (C=C) = 1635.07; (NH) = 3211.08. ^{13}C NMR δ_C (ppm): 61.01 (N-C_{ipso}); 24.45-33.27 (c-C_6H_{11}); 178.86 (C2); 176.72 (C4); 159.09 (C7); 126.61 (C_8); 132.97 (C_{8a}); 127.28-130.33 (C_6H_5). Anal. Calc. for $C_{23}H_{23}N_5$ (369g.mol^{-1}): C, 74.79; H, 6.23; N, 18.97; found C, 74.76; H, 6.20; N, 18.97 %

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