One-pot, Three-component Synthesis of 7*H*-[1,3,4]Thiadiazolo[3,2-*a*]pyridines from 2-Phenacyl-[1,3,4]thiadiazole Derivatives and Arylmethylene-cyanoacetic Acid Derivatives

Imran Ali Hashmi[a], Wolfgang Frey[b], Ivo C. Ivanov[c], and Willi Kantlehner[a, b]

[a] Fakultät Chemie/Organische Chemie, Hochschule Aalen, Beethovenstr. 1, D-73430 Aalen, Germany
[b] Institut für Organische Chemie der Universität Stuttgart, Pfaffenwaldring 55, D-70569 Stuttgart, Germany
[c] Department of Organic Chemistry, Faculty of Pharmacy, Medical University of Sofia, Dunav 2, BG-1000 Sofia, Bulgaria

Reprint requests to Prof. Dr. Willi Kantlehner. Fax: +49(0)7361-5762250.
E-mail: willi.kantlehner@htw-aalen.de

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Dedicated to Professor Horst Hartmann on the occasion of his 70th birthday

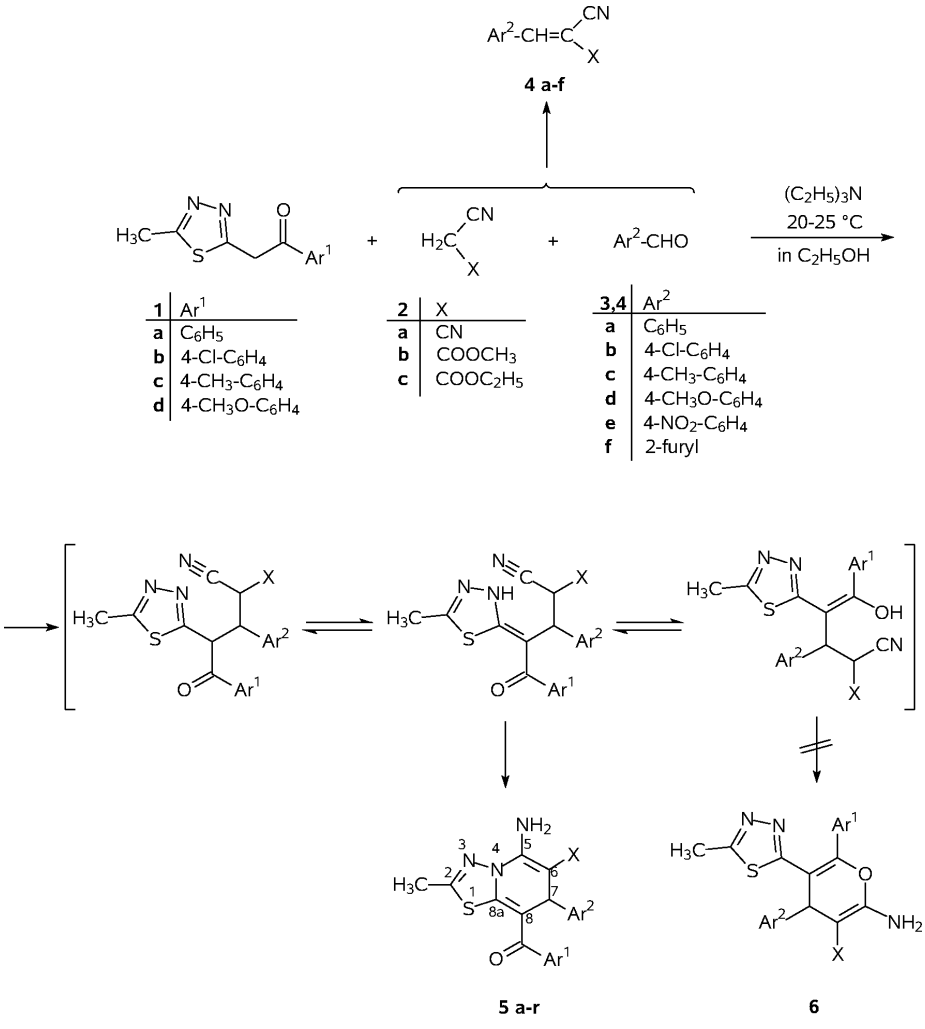
Generally, arylmethylene-cyanoacetic acid derivatives react with enols and aromatic or heteroaromatic hydroxy compounds to afford 2-amino-4*H*-pyran derivatives of type **6**. In contrast, a ring closure with the nitrogen atom of the thiadiazole ring occurs when 2-phenacyl-1,3,4-thiadiazoles (**1a** – **d**) act on derivatives of arylmethylene-cyanoacetic acid giving rise to the formation of 7*H*-[1,3,4]thiazolo[3,2-*a*]pyridine derivatives **5a** – **r**. The same products are obtained if 2-phenacyl-1,3,4-thiadiazoles react with aromatic or heteroaromatic aldehydes and cyanoacetic acid derivatives. The constitution of the novel compounds **5** has been confirmed by an X-ray analysis of **5a**.

Key words: 7*H*-[1,3,4]Thiadiazolo[3,2-*a*]pyridines, 2-Methyl-5-phenacyl-1,3,4-thiadiazoles, Aromatic Aldehydes, CH_2-Acidic Compounds, Arylmethylene-cyanoacetic Acid Derivatives

Introduction

Methylene-cyanoacetates or methylene-malononitriles show a reactivity pattern which is compatible with that of the parent carbonyl compounds (aldehydes or ketones). The compounds can electrophilically attack hydroxyarenes, hydroxyhetarenes, and enols of carbonyl derivatives. The adducts thus formed can cyclize after tautomerization to give fused 2-aminopyran derivatives, which are ketene-*O,N*-acetals, by addition of the hydroxy group to the nitrile group in the presence of a catalytic amount of a base. Methylene derivatives of nitroacetonitrile and (diethoxyphosphono)acetonitrile can also be used. By this reaction principle, several hundred heterocyclic ketene-*O,N*-acetals of a wide structural variety have been prepared [1a]. More recently, reactions of this type have been performed using microwaves, ultrasound [1b] and ionic liquids as solvents [1c, d], with no influence on the reaction outcome.

The reaction of arylmethylene-malononitriles with cyclohexanone [2a], α,β-unsaturated carbonyl compounds [2b], β-dicarbonyl compounds [3], sodium pyruvate [4] and acetylacetone [5], or with electrophilic reagents such as α-naphthol [6], 6-bromo-2-naphthol [7], hydroxyarenes [8], or with 4-hydroxy-2-pyrones and 4-hydroxy-2-pyridones [9a], 4-hydroxycoumarins [9b], 1-acetylindol-3(2*H*)-one [10] and *N*-acetonyl- or *N*-phenacyl-substituted heterocycles [11] have all been reported to form 2-aminopyran derivatives. Analogous 2-aminopyran derivatives were also obtained by a three-component reaction involving the enolisable β-dicarbonyl compound, an aldehyde and malononitrile [12]. In some cases, however, it was not pyran-2-amines but 2-aminopyridine derivatives that were obtained. Thus, the reactions of arylidene-malononitriles with enaminoketones and enhydrazinoketones gave rise mainly to the formation of 1,4-dihydropyridines [13] whereas by conjugate addition of 2-(thienylcarbonyl)acetanilides to arylmethylene-



Scheme 1.

malononitriles some polyfunctionalized pyridines [14] were prepared.

We wish to report here the one-pot synthesis of some hitherto unknown 7*H*-[1,3,4]thiadiazolo[3,2-*a*]-pyridines **5a** – **r** (Scheme 1, Table 1) by reaction of the CH-acidic phenacyl-thiadiazole derivatives **1a** – **d** with malononitrile **2a** or of cyanoacetic acid esters **2b**, **c** and aromatic aldehydes **3a** – **f**.

Results and Discussion

The synthesis of 2-methyl-5-phenacyl-1,3,4-thiadiazoles **1a** – **d** was published recently [15] and it has been shown that, as enolisable CH acids, these compounds possess ambivalent reactivity. Because of the presence of several tautomeric forms (Scheme 1), two

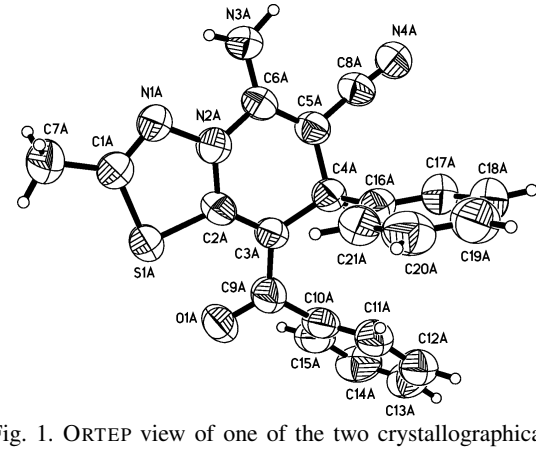


Fig. 1. ORTEP view of one of the two crystallographically independent molecules of **5a** in the crystal (displacement ellipsoids at the 50 % probability level).

Table 1. 7,8-Disubstituted 5-amino-2-methyl-7*H*-[1,3,4]thiadiazolo[3,2-*a*]pyridines **5a** – **r**[a].

Product **5**	Ar^1	X	Ar^2	Yield	M. p.	Mol. formula (mol. mass)	Elemental analysis calcd./found
a	C_6H_5	CN	C_6H_5	88	213 (dec.)	$C_{21}H_{16}N_4OS$ (372.44)	C 67.72, H 4.33, N 15.04, S 8.61 C 67.59, H 4.71, N 14.99, S 8.55
b	C_6H_5	CN	4-Cl–C_6H_4	86	194 – 197	$C_{21}H_{15}N_4OClS$ (406.89)	C 61.99, H 3.72, N 13.77, Cl 8.71, S 7.88 C 61.90, H 3.81, N 13.96, Cl 8.89, S 7.60
c	C_6H_5	CN	4-CH_3–C_6H_4	86	197 – 199	$C_{22}H_{18}N_4OS$ (386.47)	C 68.37, H 4.69, N 14.50, S 8.30 C 68.17, H 4.76, N 14.25, S 8.32
d	C_6H_5	CN	4-NO_2–C_6H_4	83	204 – 207	$C_{21}H_{15}N_5O_3S$ (417.44)	C 60.42, H 3.62, N 16.78, S 7.68 C 60.33, H 3.69, N 16.94, S 7.65
e	C_6H_5	CN	2-furyl	55	197 (dec.)	$C_{19}H_{14}N_4O_2S$ (362.41)	C 62.97, H 3.89, N 15.46, S 8.85 C 62.63, H 4.01, N 15.31, S 8.79
f	C_6H_5	COOMe	C_6H_5	83	200 – 203	$C_{22}H_{19}N_3O_3S$ (405.47)	C 65.17, H 4.72, N 10.36, S 7.91 C 65.06, H 4.92, N 10.37, S 7.45
g	C_6H_5	COOMe	4-CH_3O–C_6H_4	68	195.5 – 196	$C_{23}H_{21}N_3O_4S$ (435.50)	C 63.43, H 4.86, N 9.65, S 7.36 C 63.29, H 5.01, N 9.85, S 7.23
h	C_6H_5	COOEt	C_6H_5	84	193 – 196	$C_{23}H_{21}N_3O_3S$ (419.50)	C 65.85, H 5.05, N 10.02, S 7.64 C 65.85, H 5.07, N 10.09, S 7.84
i	C_6H_5	COOEt	4-Cl–C_6H_4	80	171 – 173	$C_{23}H_{20}N_3O_3ClS$ (453.94)	C 60.86, H 4.44, N 9.26, Cl 7.81, S 7.06 C 60.80, H 4.50, N 9.34, Cl 7.88, S 6.97
j	C_6H_5	COOEt	4-CH_3–C_6H_4	54	150 – 153	$C_{24}H_{23}N_3O_3S$ (433.52)	C 66.49, H 5.35, N 9.69, S 7.40 C 66.30, H 5.35, N 9.86, S 7.51
k	C_6H_5	COOEt	4-NO_2–C_6H_4	87	199 – 202	$C_{23}H_{20}N_4O_5S$ (464.50)	C 59.47, H 4.34, N 12.06, S 6.90 C 59.29, H 4.38, N 12.32, S 6.63
l	4-Cl–C_6H_4	CN	Ph	94	211 – 215	$C_{21}H_{15}N_4OClS$ (406.89)	C 61.99, H 3.72, N 13.77, Cl 8.71, S 7.88 C 61.80, H 3.90, N 13.57, Cl 9.28, S 7.83
m	4-Cl–C_6H_4	CN	4-Cl–C_6H_4	91	209 – 211	$C_{21}H_{14}N_4OCl_2S$ (441.33)	C 57.15, H 3.20, N 12.69, Cl 16.07, S 7.26 C 56.90, H 3.37, N 12.83, Cl 15.96, S 6.98
n	4-Cl–C_6H_4	CN	4-CH_3–C_6H_4	89	208 – 210	$C_{22}H_{17}N_4OClS$ (420.92)	C 62.78, H 4.07, N 13.31, Cl 8.42, S 7.62 C 62.67, H 4.76, N 13.04, Cl 8.37, S 7.46
o	4-Cl–C_6H_4	CN	4-NO_2–C_6H_4	96	227 – 230	$C_{21}H_{14}N_5O_3ClS$ (451.89)	C 55.82, H 3.12, N 15.50, Cl 7.85, S 7.09 C 55.77, H 3.27, N 15.76, Cl 8.00, S 7.02
p	4-CH_3–C_6H_4	CN	Ph	88	212 – 215	$C_{22}H_{18}N_4OS$ (386.47)	C 68.37, H 4.70, N 14.51, S 8.28 C 68.06, H 4.75, N 14.31, S 8.23
q	4-CH_3O–C_6H_4	CN	Ph	88	198 (dec.)	$C_{22}H_{18}N_4O_2S$ (402.47)	C 65.65, H 4.51, N 13.92, S 7.97 C 65.31, H 4.98, N 13.81, S 7.32
r	4-CH_3O–C_6H_4	CN	4-NO_2–C_6H_4	88	214 (dec.)	$C_{22}H_{17}N_5O_4S$ (447.47)	C 59.05, H 3.83, N 15.65, S 7.17 C 58.93, H 3.98, N 15.46, S 7.09

[a] All compounds recrystallized from ethanol as yellow crystals; yields in percent, m. p.'s in °C.

possible products **5** or **6** could be expected when these compounds (**1a**, **b**) are treated with arylmethylene-cyanoacetic acid derivatives of type **4** as Michael acceptors.

In the first experiment, 5-methyl-2-phenacyl-1,3,4-thiadiazole (**1a**) was allowed to react with one equivalent of benzylidene-malononitrile (**4a**) prepared according to the literature [16]. A yellow solid of **5a** was obtained on cooling. The product **5a** was isolated in a rather high yield (88 %) in a one-pot reaction by stirring the phenacyl-methyl-thiadiazole **1a** with malononitrile **2a** and benzaldehyde **3a** in ethanol for 2 h at ambient temperature in the presence of triethylamine.

In the ^{1}H NMR spectrum of this product, a broadened signal for the primary amino group and a singlet for the methine group adjacent to Ar^2 were observed at δ = 5.24 and δ = 4.88, respectively. The usual signals due to one methyl and two phenyl groups were also present in the ^{1}H and ^{13}C NMR spectra. Furthermore, the IR spectrum displayed absorption bands for a primary amino group at 3432 and 3313 cm^{-1} as well as for a cyano and a carbonyl group at 2224 and 1647 cm^{-1}, respectively. Obviously, the ^{1}H NMR and IR spectral properties of the initially prepared compound fit both isomeric structures **5a** and **6a** (X = CN, Ar^1 = Ar^2 = phenyl). The problem of the structure assignment has been solved, however, by means of an X-ray structure determination (Fig. 1, Table 2) which unambiguously confirmed the structure of **5a**. Thus, the fused bicyclic skeleton of 7*H*-[1,3,4]thiadiazolo-[3,2-*a*]pyridine is present in all the new compounds **5a** – **r**.

The 7*H*-[1,3,4]thiadiazolo[3,2-*a*]pyridine derivatives **5b**–**r** were prepared at ambient temperature by the three-component procedure as mentioned above for **5a**. The IR, ^{1}H NMR and ^{13}C NMR spectral properties of the products **5b**–**r** are fully in accordance with those of **5a** (see Experimental Section). For the reaction products **5f**–**k** obtained from the cyanoacetates **2b, c** and **1a**, no nitrile bands are present in the IR spectra. Instead, a second carbonyl band appears in the range 1619–1629 cm^{-1} for the vinylogous urethanes. Yields, molecular formulae, some physical and analytical data for compounds **5a**–**r** are summarized in Table 1.

Experimental Section

*Compound **5a** from 5-methyl-2-phenacyl[1,3,4]thiadiazole (**1a**) and benzylidene-malononitrile (**4a**)*

A mixture of 21.8 g (0.1 mol) of the thiadiazole **1a** [15] and 15.4 g (0.1 mol) of benzylidene-malononitrile (**4a**) [16] in 100 mL of ethanol was refluxed with stirring for 30 min. The color of the mixture turned to dark brown. On cooling, a yellow precipitate of **5a** was formed, which was filtered, washed with ethanol (5 × 20 mL) and air-dried. After concentrating the mother liquor *in vacuo* an additional amount of product was obtained. The whole product was recrystallized from ethanol. Yield: 31.2 g (85 %); yellow crystals of **6a** (Table 1). For crystallographic analysis, see Fig. 1 and Table 2; for spectral data, see below (after the general procedure).

*General procedure for the preparation of the compounds **5a**–**r***

A mixture of 0.05 mol of the CH_2-acidic component **2a**–**c**, 0.05 mol of the corresponding aromatic aldehyde **3a**–**f**, and 1.0 g (0.01 mol) of triethylamine in 50 mL of ethanol was stirred at ambient temperature for a period of 15 min. Then, 0.05 mol of the corresponding 5-methyl-2-phenacyl[1,3,4]thiadiazole derivative **1a**–**d** was added with stirring and the mixture was stirred for further 2 h at 20–25 °C. The completion of the reaction and the product purity were monitored by means of TLC (silica gel pre-coated plastic sheets Polygram SIL G/UV$_{254}$, Macherey-Nagel GmbH; solvent system: toluene-acetone (8 : 2); detection by UV irradiation at 254 nm). The mixture was concentrated *in vacuo* on a rotatory evaporator to approximately one third of the initial volume. The corresponding crude crystalline product **5a**–**r** precipitated. It was filtered, washed with cold ethanol, recrystallized from ethanol and air-dried.

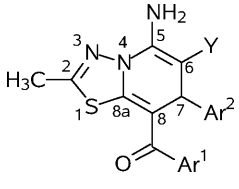


Table 2. Crystal structure data for **5a**[a].

Formula	$C_{21}H_{16}N_4OS$
M_r	372.44
Crystal size, mm^3	0.4 × 0.1 × 0.05
Crystal system	triclinic
Space group	$P\bar{1}$
a, Å	11.6762(9)
b, Å	12.5076(6)
c, Å	13.6080(10)
α, deg	98.419(6)
β, deg	103.528(6)
γ, deg	101.321(6)
V, Å^3	1855.6(2)
Z	4
D_{calcd}, g cm^{-3}	1.333
μ(CuK_α), mm^{-1}	1.695
F(000), e	776
hkl range	+13,±13,±14
$((\sin\theta)/\lambda)_{max}$, Å^{-1}	0.5616
Refl. measured	5494
Refl. unique	5210
R_{int}	0.0461
Param. refined	504
$R(F)$/w$R(F^2)$	0.137/0.274
GoF (F^2)	1.145
$\Delta\rho_{fin}$ (max/min), e Å^{-3}	0.50/−0.44

[a] CCDC 297331 contains the supplementary crystallographic data of **5a** for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

*5-Amino-8-benzoyl-2-methyl-7-phenyl-7H-[1,3,4]thiadiazolo[3,2-a]pyridine-6-carbonitrile (**5a**)*

IR (ATR): ν = 3432 and 3313 (NH_2), 2224 (CN), 1647 (C=O) cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.49 (s, 3 H, 2-CH_3), 4.88 (s, 1 H, 7-H), 5.24 (br. s, 2 H, NH_2), 6.82 (dd, ^3J = 7.7 Hz, ^4J = 1.8 Hz, 2 $H_{arom.}$), 7.1–7.4 (m, 8 $H_{arom.}$). – ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 15.5 (2-CH_3), 41.3 (C-7), 64.0 (C-6), 102.1 (C-8), 119.7 (CN), 146.8 (C-8a), 150.5 (C-2), 155.4 (C-5), 126.6 (4 $C_{arom.}$) 127.1, 128.2 (2 C), 128.7 (2 C), 130.1, 139.0, 145.1 (total 12 $C_{arom.}$), 191.4 (8-C=O).

*5-Amino-8-benzoyl-7-(4-chlorophenyl)-2-methyl-7H-[1,3,4]thiadiazolo[3,2-a]pyridine-6-carbonitrile (**5b**)*

IR (ATR): ν = 3467 and 3318 (NH_2), 2186 (CN), 1652 (C=O) cm^{-1}. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.48 (s, 3 H, 2-CH_3), 4.87 (s, 1 H, 7-H), 5.31 (br. s, 2 H, NH_2), 6.72 (d, J = 8.5 Hz, 2 $H_{arom.}$), 7.10 (d, J = 8.5 Hz, 2 $H_{arom.}$), 7.30 (m_c, 5 $H_{arom.}$). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.5 (2-CH_3), 40.9 (C-7), 63.5 (C-6), 150.6 (C-2), 155.5 (C-5),

101.7 (C-8), 119.5 (CN), 146.9 (C-8a), 126.5, 128.1, 128.3, 128.8, 130.2, 132.8, 138.9, 143.6 (total 12 $C_{arom.}$), 191.2 (8-C=O).

*5-Amino-8-benzoyl-2-methyl-7-(4-methylphenyl)-7H-[1,3,4]thiadiazolo[3,2-a]pyridine-6-carbonitrile (**5c**)*

IR (ATR): ν = 3458 and 3303 (NH_2), 2195 (CN), 1652 (C=O) cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.24 (s, 3 H, Ar^2CH_3), 2.47 (s, 3 H, 2-CH_3), 4.83 (s, 1 H, 7-H), 5.25 (br. s, 2 H, NH_2), 6.72 (d, J = 8.0 Hz, 2 $H_{arom.}$), 6.95 (d, J = 8.0 Hz, 2 $H_{arom.}$), 7.2 – 7.5 (m, 5 $H_{arom.}$, *Ph*C=O). – ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 15.5 (2-CH_3), 21.0 (Ar^2CH_3), 40.8 (C-7), 64.1 (C-6), 102.1 (C-8), 119.8 (CN), 146.8 (C-8a), 150.4 (C-2), 155.3 (C-5), 126.4 (2 C), 126.7 (2 C), 128.2 (2 C), 129.4 (2 C), 130.1, 136.7, 139.0, 142.3 (total 12 $C_{arom.}$), 191.3 (8-C=O).

*5-Amino-8-benzoyl-2-methyl-7-(4-nitrophenyl)-7H-[1,3,4]-thiadiazolo[3,2-a]pyridine-6-carbonitrile (**5d**)*

IR (ATR): ν = 3450 and 3341 (NH_2), 2184 (CN), 1651 (C=O) cm^{-1}. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.52 (s, 3 H, 2-CH_3), 5.06 (s, 1 H, 7-H), 5.39 (br. s, 2 H, NH_2), 7.15, 7.30 (2 × m, 3 $H_{arom.}$ + 2 $H_{arom.}$), 8.00 (d, J = 8.7 Hz, 2 $H_{arom.}$), 6.59 (d, J = 8.7 Hz, 2 $H_{arom.}$). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.5 (2-CH_3), 41.5 (C-7), 63.0 (C-6), 100.9 (C-8), 119.1 (CN), 147.1 (C-8a), 151.6 (C-2), 155.8 (C-5), 124.0, 126.4, 127.6, 128.5, 130.4, 138.8, 146.8, 151.1 (total 12 $C_{arom.}$), 191.0 (8-C=O).

*5-Amino-8-benzoyl-7-(2-furyl)-2-methyl-7H-thiadiazolo-[3,2-a]pyridine-6-carbonitrile (**5e**)*

IR (ATR): ν = 3458 and 3433 (NH_2), 2192 (CN), 1660 (C=O) cm^{-1}. – ^{1}H NMR (250 MHz, $CDCl_3$): δ= 2.49 (s, 3 H, 2-CH_3), 4.99 (s, 1 H, 7-H), 5.34 (br. s, 2 H, NH_2), 5.65 (d, J_1 = 3.2 Hz, 1 $H_{arom.}$, furyl), 6.14 (dd, J_1 = 3.2, J_2 = 1.6 Hz, 1 $H_{arom.}$, furyl), 7.20 (d, J_2 = 1.6 Hz, 1 $H_{arom.}$, furyl), 7.37 (m_c, 5 $H_{arom.}$, *Ph*C=O). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.5 (2-CH_3), 35.2 (C-7), 60.5 (C-6), 99.4 (C-8), 105.4 ($C_{arom.}$, furyl), 110.2 ($C_{arom.}$, furyl), 119.5 (CN), 126.8 (2 C), 128.4 (2 C), 130.3, 138.8 (total 6 $C_{arom.}$, Ph), 148.1 (C-8a), 151.1 (C-2), 155.6 (C-5), 156.1 ($C_{arom.}$, furyl), 142.2 ($C_{arom.}$, furyl), 190.9 (8-C=O).

*Methyl 5-amino-8-benzoyl-2-methyl-7-phenyl-7H-[1,3,4] thiadiazolo[3,2-a]pyridine-6-carboxylate (**5f**)*

IR (ATR): ν = 3489 and 3306 (NH_2), 1676 (C=O), 1622 (C=O, ester) cm^{-1}. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.48 (s, 3 H, 2-CH_3), 3.62 (s, 3 H, OCH_3), 5.28 (s, 1 H, 7-H), 6.77, 7.03 (2 × m, 2 $H_{arom.}$, 3 $H_{arom.}$, *Ph*C=O), 7.35 (m, 5 $H_{arom.}$, 7-Ph). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.6 (2-CH_3), 39.4 (C-7), 50.9 (OCH_3), 81.5 (C-6), 104.4 (C-8), 148.0 (C-8a), 150.4 (C-2), 155.1 (C-5), 169.1 (6-C=O), 191.3 (8-C=O), 126.2, 126.8, 127.1, 128.0, 128.1, 130.0, 139.4, 146.7 (total 12 $C_{arom.}$).

*Methyl 5-amino-8-benzoyl-7-(4-methoxyphenyl)-2-methyl-7H-[1,3,4]thiadiazolo[3,2-a]pyridine-6-carboxylate (**5g**)*

IR (ATR), ν = 3479 and 3301 (NH_2), 1679 (C=O), 1627 (C=O, ester) cm^{-1}. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.49 (s, 3 H, 2-CH_3), 3.62 (s, 3 H, OCH_3), 3.70 (s, 3 H, OCH_3), 5.21 (s, 1 H, 7-H), 6.69 and 6.59 (2 × d, J = 8.8 Hz, 2 × 2 $H_{arom.}$, 7-C_6H_4), 7.41 (m, 5 $H_{arom.}$, *Ph*C=O). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.7 (2-CH_3), 38.5 (C-7), 50.9 (OCH_3), 55.1 (OCH_3), 81.6 (C-6), 104.8 (C-8), 148.0 (C-8a), 150.2 (C-2), 155.2 (C-5), 113.4, 127.2, 127.8, 128.2, 129.9, 139.4, 139.5, 157.9 (total 12 $C_{arom.}$), 169.5 (6-C=O), 191.4 (8-C=O).

*Ethyl 5-amino-8-benzoyl-2-methyl-7-phenyl-7H-[1,3,4] thiadiazolo[3,2-a]pyridine-6-carboxylate (**5h**)*

IR (ATR): ν = 3489 and 3301 (NH_2), 1675 (C=O), 1626 (C=O, ester) cm^{-1}. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.15 (t, 3 H, OCH_2CH_3), 2.48 (s, 3 H, 2-CH_3), 4.10 (q, 2 H, OCH_2), 5.31 (s, 1 H, 7-H), 6.75, 7.04, 7.38 (3 × m, 2 H, 4 H, 4 H, 7-Ph, *Ph*C=O). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.2 (OCH_2CH_3), 15.6 (2-CH_3), 39.4 (C-7), 59.5 (OCH_2), 81.5 (C-6), 104.4 (C-8), 148.0 (C-8a), 150.4 (C-2), 155.1 (C-5), 126.2, 126.9, 127.2, 128.0, 128.1, 130.0, 139.5, 146.8 (total 12 $C_{arom.}$), 169.1 (6-C=O), 191.3 (8-C=O).

*Ethyl 5-amino-8-benzoyl-7-(4-chlorophenyl)-2-methyl-7H-[1,3,4]thiadiazolo[3,2-a]pyridine-6-carboxylate (**5i**)*

IR (ATR): ν = 3425 and 3302 (NH_2), 1664 (C=O, ketone), 1620 (C=O, ester) cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.14 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 2.50 (s, 3 H, 2-CH_3), 4.08 (q, J = 7.1 Hz, 2 H, OCH_2), 5.28 (s, 1 H, 7-H), 7.00 (d, J = 8.5 Hz, 2 $H_{arom.}$), 6.65 (d, J = 8.5 Hz, 2 $H_{arom.}$), 7.35 (m, 5 $H_{arom.}$ + NH_2). – ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 14.3 (OCH_2CH_3), 15.7 (2-CH_3), 39.2 (C-6), 59.6 (OCH_2), 81.2 (C-6), 104.1 (C-8), 147.9 (C-8a), 150.4 (C-2), 155.2 (C-5), 127.0 (2 C), 128.0 (2 C), 128.3 (2 C), 128.4 (2 C), 130.1, 131.8, 139.3, 145.4 (total 12 $C_{arom.}$), 168.9 (6-C=O), 191.3 (8-C=O).

*Ethyl 5-amino-8-benzoyl-2-methyl-7-(4-methylphenyl)-7H-[1,3,4]thiadiazolo[3,2-a]pyridin-6-carboxylate (**5j**)*

IR (ATR): ν = 3426 and 3303 (NH_2), 1664 (C=O, ketone), 1619 (C=O, ester) cm^{-1}. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.71 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 2.21 (s, 3 H, Ar^2CH_3), 2.49 (s, 3 H, 2-CH_3), 4.10 (q, J = 7.1 Hz, 3 H, OCH_2), 5.29 (s, 1 H, 7-H), 6.66 (d, J = 7.9 Hz, 2 $H_{arom.}$), 6.85 (d, J = 7.9 Hz, 2 $H_{arom.}$), 6.7 – 7.2 (br., 2 H, NH_2), 7.38 (m_c,

5 $H_{arom.}$, *Ph*C=O). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.3 (OCH_2CH_3), 15.7 (2-CH_3), 38.9 (C-7), 59.5 (OCH_2), 81.6 (C-6), 104.6 (C-8), 148.1 (C-8a), 150.3 (C-2), 155.1 (C-5), 126.8, 127.3, 128.1, 128.7, 130.0, 135.6, 139.4, 143.9 (total 12 $C_{arom.}$), 169.1 (6-C=O), 191.4 (8-C=O).

*Ethyl 5-amino-8-benzoyl-2-methyl-7-(4-nitrophenyl)-7H-[1,3,4]thiadiazolo[3,2-a]pyridine-6-carboxylate (**5k**)*

IR (ATR): ν = 3392 and 3287 (NH_2), 1671 (C=O, ketone), 1620 (C=O, ester) cm^{-1}. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.13 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 2.53 (s, 3 H, 2-CH_3), 4.07 (q, J = 7.1 Hz, 2 H, OCH_2), 5.43 (s, 1 H, 7-H), 6.85 (d, J = 8.7 Hz, 2 $H_{arom.}$), 7.90 (d, J = 8.7 Hz, 2 $H_{arom.}$), 6.7 – 8.0 (br., 2 H, NH_2), 7.2 – 7.5 (m, 5 $H_{arom.}$, *Ph*C=O). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.3 (OCH_2CH_3), 15.7 (2-CH_3), 40.0 (C-7), 59.8 (OCH_2), 80.4 (C-6), 103.2 (C-8), 148.0 (C-8a), 151.0 (C-2), 155.5 (C-5), 123.3 (2 C), 126.9 (2 C), 127.9 (2 C), 128.5 (2 C), 130.4, 139.2, 146.2, 153.9 (total 12 $C_{arom.}$), 168.6 (6-C=O), 191.0 (8-C=O).

*5-Amino-8-(4-chlorobenzoyl)-2-methyl-7-phenyl-7H-[1,3,4]thiadiazolo[3,2-a]pyridine-6-carbonitrile (**5l**)*

IR (ATR): ν = 3466 and 3314 (NH_2), 2187 (CN), 1652 (C=O) cm^{-1}. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.53 (s, 3 H, 2-CH_3), 4.82 (s, 1 H, 7-H), 5.21 (br. s, 2 H, NH_2), 6.86 (m_c, 2 $H_{arom.}$, Ph), 7.13 (d, J = 8.6 Hz, 2 $H_{arom.}$, Ar^1), 7.13 – 7.27 (m, 3 $H_{arom.}$, Ph), 7.27 (d, J = 8.6 Hz, 2 $H_{arom.}$, Ar^1). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.5 (2-CH_3), 41.3 (C-7), 64.3 (C-6), 101.7 (C-8), 119.5 (CN), 151.0 (C-2), 155.5 (C-5), 146.6 (C-8a), 126.6, 127.3, 128.2, 128.5, 128.9, 136.2, 137.4, 144.9 (total 12 $C_{arom.}$), 190.0 (8-C=O).

*5-Amino-8-(4-chlorobenzoyl)-7-(4-chlorophenyl)-2-methyl-7H-[1,3,4]thiadiazolo[3,2-a]pyridine-6-carbonitrile (**5m**)*

IR (ATR): ν = 3459 and 3301 (NH_2), 2193 (CN), 1657 (C=O) cm^{-1}. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.50 (s, 3 H, 2-CH_3), 4.82 (s, 1 H, 7-H), 5.33 (br. s, 2 H, NH_2), 6.77 (d, J = 8.4 Hz, 2 $H_{arom.}$, Ar^1), 7.14 (d, J = 8.4 Hz, 4 $H_{arom.}$, $Ar^1 + Ar^2$), 7.29 (d, J = 8.4 Hz, 2 $H_{arom.}$, Ar^2). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.5 (2-CH_3), 40.9 (C-7), 63.7 (C-6), 101.4 (C-8), 119.3 (CN), 151.1 (C-2), 155.6 (C-5), 146.7 (C-8a), 128.0 (2 C), 128.1 (2 C), 128.6 (2 C), 128.9 (2 C), 133.1, 136.3, 137.3, 143.5 (total 12 $C_{arom.}$), 189.8 (8-C=O).

*5-Amino-8-(4-chlorobenzoyl)-2-methyl-7-(4-methylphenyl)-7H-thiadiazolo[3,2-a]pyridine-6-carbonitrile (**5n**)*

IR (ATR): ν = 3457 and 3301 (NH_2), 2194 (CN), 1651 (C=O) cm^{-1}. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.25 (s, 3 H, Ar^2CH_3), 2.48 (s, 3 H, 2-CH_3), 4.77 (s, 1 H, 7-H), 5.28 (br. s, 2 H, NH_2), 6.74 (d, J = 8.4 Hz, 2 $H_{arom.}$, Ar^1), 6.98 (d, J = 8.4 Hz, 2 $H_{arom.}$, Ar^1), 7.15 (d, J = 8.4 Hz, 2 $H_{arom.}$, Ar^2), 7.25 (d, J = 8.4 Hz, 2 $H_{arom.}$, Ar^2). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.6 (2-CH_3), 21.1 (PhCH_3), 40.9 (C-7), 64.3 (C-6), 101.9 (C-8), 119.7 (CN), 146.7 (C-8a), 151.0 (C-2), 155.5 (C-5), 126.5 (2 C), 128.3 (2 C), 128.5 (2 C), 129.6 (2 C), 136.2, 136.9, 137.5, 142.2 (total 12 $C_{arom.}$), 189.9 (8-C=O).

*5-Amino-8-(4-chlorobenzoyl)-2-methyl-7-(4-nitrophenyl)-7H-[1,3,4]thiadiazolo[3,2-a]pyridine-6-carbonitrile (**5o**)*

IR (ATR): ν = 3448 and 3338 (NH_2), 2184 (CN), 1653 (C=O) cm^{-1}. – ^{1}H NMR (250 MHz, [D_6]DMSO): δ = 2.55 (s, 3 H, 2-CH_3), 5.05 (s, 1 H, 7-H), 7.05 (br. s, 2 H, NH_2), 7.06 (d, J = 8.7 Hz, 2 $H_{arom.}$, Ar^1), 7.25 (d, J = 8.4 Hz, 2 $H_{arom.}$, Ar^2), 7.38 (d, J = 8.4 Hz, 2 $H_{arom.}$, Ar^2), 8.04 (d, J = 8.7 Hz, 2 $H_{arom.}$, Ar^1). – ^{13}C NMR (62.9 MHz, [D_6]DMSO): δ = 15.1 (2-CH_3), 41.2 (C-7), 60.3 (C-6), 100.0 (C-8), 119.6 (CN), 146.1 (C-8a), 152.6 (C-2), 155.1 (C-5), 123.8 (2 C), 127.8 (2 C), 128.2 (2 C), 128.4 (2 C), 134.6, 137.8, 146.1, 151.8 (total 12 $C_{arom.}$), 188.2 (8-C=O).

*5-Amino-2-methyl-8-(4-methylbenzoyl)-7-phenyl-7H-[1,3,4]thiadiazolo[3,2-a]pyridine-6-carbonitrile (**5p**)*

IR (ATR): ν = 3465 and 3314 (NH_2), 2187 (CN), 1651 (C=O, ketone) cm^{-1}. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.35 (s, 3 H, Ar^1CH_3), 2.49 (s, 3 H, 2-CH_3), 4.92 (s, 1 H, 7-H), 5.20 (br. s, 2 H, NH_2), 7.20 (m_c, 9 $H_{arom.}$, $Ar^1 + Ar^2$). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.5 (2-CH_3), 21.5 (Ar^1CH_3), 41.2 (C-7), 63.8 (C-6), 102.1 (C-8), 119.7 (CN), 147.0 (C-8a), 150.3 (C-2), 155.4 (C-5), 126.6, 127.0, 127.1, 128.7, 128.9, 136.1, 140.57, 145.1 (total 12 $C_{arom.}$), 191.2 (8-C=O).

*5-Amino-8-(4-methoxybenzoyl)-2-methyl-7-phenyl-7H-[1,3,4]thiadiazolo[3,2-a]pyridine-6-carbonitrile (**5q**)*

IR (ATR): ν = 3463 and 3321 (NH_2), 2187 (CN), 1657 (C=O, ketone) cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.47 (s, 3 H, 2-CH_3), 3.81 (s, 3 H, OMe), 4.97 (s, 1 H, 7-H), 5.28 (s, 2 H, NH_2), 6.82 (d, J = 8.5 Hz, 2 $H_{arom.}$), 6.91 (d, J = 7.2 Hz, 2 $H_{arom.}$), 7.19 (m_c, 3 $H_{arom.}$), 7.29 (d, J = 8.5 Hz, 2 $H_{arom.}$). – ^{13}C NMR (125,8 MHz, $CDCl_3$): δ = 15.2 (2-CH_3), 41.3 (C-7), 55.4 (OMe), 63.4 (C-6), 102.1 (C-8), 119.9 (CN), 147.2 (C-8a), 150.4 (C-2), 155.4 (C-5), 113.6 (2 C), 126.5 (2 C), 127.1, 128.8 (2 C), 129.0 (2 C), 131.3, 145.1, 161.3 (total 12 $C_{arom.}$), 190.3 (8-C=O).

*5-Amino-8-(4-methoxybenzoyl)-2-methyl-7-(4-nitrophenyl)-7H-[1,3,4]thiadiazolo[3,2-a]pyridine-6-carbonitrile (**5r**)*

IR (ATR): ν = 3464 and 3322 (NH_2), 2186 (CN), 1659 (C=O) cm^{-1}. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.53 (s, 3 H, 2-CH_3), 3.84 (s, 3 H, OMe), 5.17 (s, 1 H, 7-H), 5.28 (br. s, 2 H, NH_2), 6.85 (d, J = 8.8 Hz, 2 H, Ar^1), 7.03 (d,

J = 8.8 Hz, 2 H, Ar^2), 7.26 (d, J = 8.8 Hz, 2 H, Ar^1), 8.04 (d, J = 8.8 Hz, 2 H, Ar^2). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.5 (2-CH_3), 41.3 (C-7), 55.3 (OMe), 63.4 (C-6), 102.1 (C-8), 119.9 (CN), 147.2 (C-8a), 150.3 (C-2), 155.4 (C-5), 113.6, 126.5, 127.1, 128.8, 129.0, 131.4, 145.1, 161.3 (total 12 $C_{arom.}$), 190.3 (8-C=O).

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