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Efficient Synthesis and Dehydration Reaction of Trichloromethylated 2-(3-Phenyl-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl)-4-aryl-5-alkylthiazoles

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ABSTRACT: *A convenient method for the synthesis of a novel series of 11, specifically substituted, noncondensed 5,5-bicycles 2-[3-phenyl-5-hydroxy-5-trichloromethyl-4,5-dihydro-1*H*-pyrazol-1-yl]-4-aryl-5-alkylthiazoles (***3a–k***; 65–94% yield) from the reactions of 3-phenyl-5-hydroxy-5-trichloromethyl-4,5-dihydro-1*H*-1-pyrazolethiocarboxyamide (***1***) with substituted 2-bromo-4′-acetophenones (***2a–f***) and 2-bromo-4′-propiophenones (***2g–k***) is reported. Dehydration of compounds* **3a–k** *with a mixture of concentrated sulfuric acid/chloroform furnished the corresponding 2-[3-phenyl-5-trichloromethyl-1*H*-pyrazol-1-yl]-4-aryl-5-alkylthiazoles (***4a–k***) in good yields (61–93%).* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:132–137, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10113

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INTRODUCTION

Recently, a great interest has been directed toward the synthesis of trifluoromethyl-substituted heteroaromatic compounds, partly because of the unique biological properties imparted by the fluorine [1]. On the other hand, trichloromethylated heterocycles are although relatively rare but promising templates for biological activity. For example, trichloromethyl substituted benzodiazepines [2,3], 4,5-dihydro-pyrazoles [4], and quinazolines [5] have exhibited activity as acetylcholinesterase and ATPDase inhibitors [2], anxiolytics [3], anti-inflammatories [4], analgesics [4], and cyclin-dependent kinases (CDKs) inhibitors [5] in the cell cycle proteins. Thus, the possibility to obtain trichloromethyl-substituted heterocycles [6–8] combined with the versatility of the trichloromethyl group as precursor of carboxyl groups [9–11], prompted us to devote special attention to the chemistry of the trichloromethyl-contained building blocks. Although many methods for the synthesis of thiazoles and pyrazoles have been reported [12–18], the synthesis of noncondensed 5,5-bicycles, as 2-(1*H*-pyrazol-1-yl)-thiazoles, was little explored. In the literature we found just a few methods to obtain trifluoromethylated pyrazolyl-thiazole system [19–23] and none of these methods have been used to synthesize trichloromethylated derivatives.

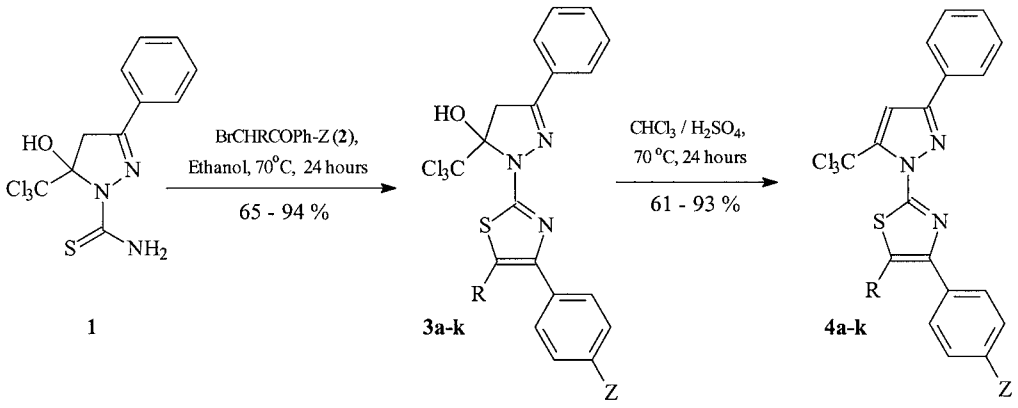
One of the better methods to introduce a trichloromethyl group into heterocycles is based on the trichloromethylated building block approach. This approach relies on the trichloroacetylation of enol ethers or acetals to give, in one step and good yields, β-alkoxyvinyl trichloromethyl ketones, which proved to be useful building blocks for the synthesis of five [7,24–27], six [8,28–30], and seven [9,31] membered trichloromethylated heterocyclic compounds.

In a recent work we have reported a method that provides the regiospecific synthesis of 5-trihalomethyl-4,5-dihydro-1H-pyrazoles in high yield from the reaction of β-alkoxyvinyl trihalomethyl ketones with semicarbazide or thiosemicarbazide [24,32]. Specifically, it was shown that the reaction of 4-alkoxy-1,1,1-trichloro-alk-3-en-2-ones with thiosemicarbazide gave 3-alkyl- or 3-(4-substituted phenyl)-5-hydroxy-5-trichloromethyl-1*H*-1-pyrazolethiocarboxyamide (**1**) in excellent yields [24] and our attempt to perform the dehydration of **1**, under acidic conditions, furnished a complex mixture of products. These conditions do not allow to obtain the pyrazol ring containing a trichloromethyl and a thiocarboxyamide substituent.

The aim of the present work was to obtain 2-[3-phenyl-5-hydroxy-5-trichloromethyl-4,5-dihydro-1*H*-pyrazol-1-yl]-4-aryl-5-alkylthiazoles (**3a–k**) from the reaction of **1** with various 2-bromoacetophenones (**2a–f**) and 2-bromopropiophenones (**2g–k**), using the trichloromethylated building block approach (Scheme 1). Subsequently, thiazoles **3a–k** was submitted to dehydration to obtain a new series of bis-aromatic 2-(3-phenyl-5-trichloromethyl-1*H*-pyrazol-1-yl)-4-aryl-5-alkylthiazoles (**4a–k**).

RESULTS AND DISCUSSION

Starting from **1**, all cyclocondensation reactions with 2-bromoketones (**2**) were carried out in ethanol for 24 h at 70°C for **3a–k**. Normally, the bicycles crystallized in the course of the reaction, and then they are filtered off and obtained in good purity by evaporation of solvent residue under reduced pressure (65–94 %). A subsequent reaction allowed to synthesize another series of 2-[3-phenyl-5-trichloromethyl-1*H*-pyrazol-1-yl]-4-aryl-5-alkylthiazoles (**4a–k**), which was obtained in good yield (61–93%), from the dehydration of **3a–k** carried out in a solution of concentrated sulfuric acid in chloroform under reflux for 24 h. The reactions were neutralized and compounds **4** were isolated by extraction with chloroform. Compounds **4** were obtained in good purity by evaporation of solvent residue under reduced pressure. In contrast with compound **1**, compound **4** does not show the thioamide bond at N-1, and the new bond between the heterocycles **3** is extremely strong and allows the dehydration reaction in sulfuric acid medium. It is interesting that the CCl_3



1-4	a	b	c	d	e	f	g	h	i	j	k
R	H	H	H	H	H	H	CH_3	CH_3	CH_3	CH_3	CH_3
Z	H	CH_3	OCH_3	Cl	Br	NO_2	H	CH_3	OCH_3	Cl	Br

SCHEME 1 Synthetic route and structures of compounds **1–4**.

TABLE 1 Selected Physical Data of **3**

Compound	*Yield (%)*[a]	*mp (°C)*[b]	*Molecular Formula (g/mol)*	*Calcd*[c] *C*	*H*	*N*
3a	94	153–155	$C_{19}H_{14}N_3OSCl_3$ 438.76	52.01 (51.93)	3.22 (3.17)	9.58 (9.93)
3b	70	172–174	$C_{20}H_{16}N_3OSCl_3$ 452.78	53.05 (53.05)	3.56 (3.46)	9.28 (9.54)
3c	84	156–158	$C_{20}H_{16}N_3O_2SCl_3$ 468.78	51.24 (51.30)	3.44 (3.36)	8.96 (9.28)
3d	90	189–191	$C_{19}H_{13}N_3OSCl_4$ 473.20	48.23 (48.31)	2.77 (2.70)	8.88 (9.23)
3e	86	203–205	$C_{19}H_{13}N_3OSBrCl_3$ 517.65	44.09 (44.15)	2.53 (2.53)	8.12 (8.47)
3f	82	207–209	$C_{19}H_{13}N_4O_3SCl_3$ 483.75	47.17 (47.08)	2.71 (2.67)	11.58 (11.80)
3g	65	171–173	$C_{20}H_{16}N_3OSCl_3$ 452.78	53.05 (53.05)	3.56 (3.49)	9.28 (9.63)
3h	66	145–147	$C_{21}H_{18}N_3OSCl_3$ 466.81	54.03 (54.13)	3.89 (3.79)	9.00 (9.27)
3i	65	155–157	$C_{21}H_{18}N_3O_2SCl_3$ 482.81	52.24 (52.14)	3.76 (3.62)	8.70 (8.56)
3j	79	157–159	$C_{20}H_{15}N_3OSCl_4$ 487.23	49.30 (49.57)	3.10 (2.98)	8.62 (8.96)
3k	81	161–163	$C_{20}H_{15}N_3OSBrCl_3$ 531.68	45.18 (45.34)	2.84 (2.74)	7.90 (8.26)

[a]Yield of isolated compounds.
[b]The melting points are uncorrected.
[c]Values in parenthesis indicate found values.

TABLE 2 Selected Physical Data of **4**

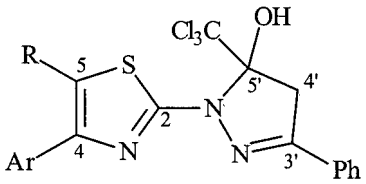
Compound	*Yield (%)*[a]	*mp (°C)*[b]	*Molecular Formula (g/mol)*	*Calcd*[c] *C*	*H*	*N*
4a	65	123–125	$C_{19}H_{12}N_3SCl_3$ 420.74	54.24 (54.53)	2.87 (2.92)	9.99 (10.25)
4b	65	171–173	$C_{20}H_{14}N_3SCl_3$ 434.77	55.25 (55.08)	3.25 (3.33)	9.66 (9.80)
4c	70	193–195	$C_{20}H_{14}N_3OSCl_3$ 450.76	53.29 (53.34)	3.13 (3.23)	9.32 (8.71)
4d	93	175–177	$C_{19}H_{11}N_3SCl_4$ 455.18	50.14 (50.19)	2.44 (2.51)	9.23 (9.53)
4e	61	186–188	$C_{19}H_{11}N_3SBrCl_3$ 499.63	45.67 (45.29)	2.22 (2.46)	8.41 (8.26)
4f	73	218–220	$C_{19}H_{11}N_4O_2SCl_3$ 465.74	49.00 (48.63)	2.38 (2.78)	12.03 (11.82)
4g	83	149–151	$C_{20}H_{14}N_3SCl_3$ 434.77	55.25 (55.50)	3.25 (3.66)	9.66 (9.27)
4h	71	158–160	$C_{21}H_{16}N_3SCl_3$ 448.79	56.20 (56.59)	3.59 (3.20)	9.36 (9.66)
4i	73	177–179	$C_{21}H_{16}N_3OSCl_3$ 464.79	54.27 (54.07)	3.47 (3.42)	9.04 (9.24)
4j	91	181–183	$C_{20}H_{13}N_3SCl_4$ 469.21	51.20 (51.52)	2.79 (2.90)	8.96 (9.26)
4k	74	178–180	$C_{20}H_{13}N_3SBrCl_3$ 513.66	46.77 (47.02)	2.55 (2.84)	8.18 (8.14)

[a]Yield of isolated compounds.
[b]The melting points are uncorrected.
[c]Values in parenthesis indicate found values.

substituent was not converted into carboxyl group, in contrast to the dehydration reaction described by Spiegler [7], which obtained isoxazole-5-carboxylic acid from the reaction of 5-trichloromethylisoxazole with 96% sulfuric acid at 110°C for 4–12 h. Compounds **1** [24] and **2** [33] were prepared according to the literature procedures. All reactions are presented in Scheme 1 and the best results of these reactions and selected physical data are presented in Tables 1 and 2. The best reaction conditions are presented in the experimental part. The ^{1}H and ^{13}C NMR spectral data are presented and in Tables 3 and 4.

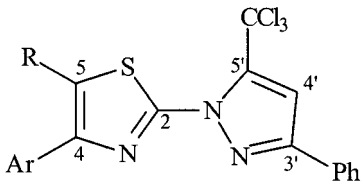
We consider the presented cyclocondensation and the subsequent dehydration reaction a useful

TABLE 3 Selected ^{1}H and ^{13}C MNR Spectral Data of **3**



Compound	*^{1}H NMR ($CDCl_3$/TMS, δ, J (Hz)/^{13}C NMR ($CDCl_3$/TMS, δ)*
3a	7.78–7.73, 7.45–7.23 (2m, 10H, Ar—H), 6.96 (s, 1H, H5), 4.10 (d, 1H, $J = 18.6$, H4′a), 3.77 (d, 1H, $J =$ 18.6, H4′b). 166.08 (C3′), 154.39 (C4), 150.29 (C2), 133.81, 130.75, 130.09, 128.82, 128.71, 128.11, 126.61, 125.85 (12C, Ar—C), 104.87 (C5), 104.00 (CCl_3), 102.52 (C5′), 47.44 (C4′).
3b	7.75–7.61, 7.42–7.39, 7.19–7.15 (3m, 9H, Ar—H), 6.86 (s, 1H, H5), 4.08 (d, 1H, $J = 18.7$, H4′a), 3.74 (d, 1H, $J = 18.7$, H4′b), 2.34 (s, 3H, CH_3). 165.94 (C3′), 154.23 (C4), 150.29 (C2), 137.92, 131.07, 130.03, 129.45, 129.34, 128.76, 126.54, 125.72 (12C, Ar—C), 104.43 (C5), 104.01 (CCl_3), 102.46 (C5′), 47.35 (C4′), 21.21 (CH_3).
3c	8.48 (s, 1H, OH), 7.83–7.79, 7.50–7.47, 6.98–6.94 (3m, 9H, Ar—H), 7.38 (s, 1H, H5), 4.13 (d, 1H, $J = 18.6$, H4′a), 3.89 (d, 1H, $J = 18.6$, H4′b), 3.77 (s, 3H, p-OCH_3). 163.78 (C4), 158.97 (C3′), 150.11(C2), 153.17, 130.55, 129.97, 128.87, 127.11, 127.05, 126.42, 114.00 (12C, Ar—C), 104.79 (C5), 103.69 (CCl_3), 102.23 (C5′), 55.10 (p-OCH_3), 47.17 (C4′).
3d	7.78–7.66, 7.46–7.24 (2m, 9H, Ar—H), 6.95 (s, 1H, H5), 4.11 (d, 1H, $J = 18.8$, H4′a), 3.76 (d, 1H, $J = 18.8$, H4′b). 165.46 (C3′), 153.97 (C4), 148.53 (C2), 133.01, 131.85, 130.30, 129.33, 128.29, 128.24, 126.57, 126.04 (12C, Ar—C), 105.10 (C5), 103.37 (CCl_3), 101.85 (C5′), 46.85 (C4′).
3e	8.46 (s, 1H, OH), 8.00–7.80, 7.62–7.49 (2m, 9H, Ar—H), 7.64 (s, 1H, H5), 4.16 (d, 1H, $J = 19.1$, H4′a), 3.90 (d, 1H, $J = 19.1$, H4′b). 163.78 (C3′), 153.12 (C4), 149.20 (C2), 133.48, 131.61, 130.57, 129.74, 128.75, 127.79, 126.12, 120.72 (12C, Ar—C), 107.79 (C5), 103.57 (CCl_3), 102.26 (C5′), 47.24 (C4′).
3f	8.27–8.23, 7.92–7.74, 7.48–7.25 (3m, 9H, Ar—H), 7.19 (s, 1H, H5), 4.13 (d, 1H, $J = 18.8$, H4′a), 3.80 (d, 1H, $J = 18.8$, H4′b). 166.51 (C3′), 154.97 (C4), 147.12 (C2), 148.22, 139.61, 131.01, 129.81, 128.99, 126.66, 126.31, 124.19 (12C, Ar—C), 108.83 (C5), 103.77 (CCl_3), 102.41 (C5′), 47.84 (C4′).
3g	7.74–7.55, 7.43–7.22 (2m, 10H, Ar—H), 4.06 (d, 1H, $J = 18.6$, H4′a), 3.73 (d, 1H, $J = 18.6$, H4′b), 2.47 (s, 3H, CH_3). 162.60 (C3′), 153.78 (C4), 144.96 (C2), 134.47, 130.56, 130.20, 128.76, 128.31, 128.13, 127.44, 126.49 (12C, Ar—C), 120.03 (C5), 104.11 (CCl_3), 102.65 (C5′), 47.37 (C4′), 12.20 (CH_3).
3h	7.76–7.71, 7.48–7.41, 7.23–7.19 (3m, 9H, Ar—H), 4.06 (d, 1H, $J = 18.8$, H4′a), 3.74 (d, 1H, $J = 18.8$, H4′b), 2.46 (s, 3H, CH_3), 2.38 (s, 3H, p-CH_3). 162.53 (C3′), 153.67 (C4), 145.05 (C2), 137.25, 131.72, 130.52, 130.28, 129.01, 128.76, 128.05, 126.49 (12C, Ar—C), 119.40 (C5), 104.16 (CCl_3), 102.67 (C5′), 47.40 (C4′), 21.21 (p-CH_3), 12.20 (CH_3).
3i	7.76–7.71, 7.53–7.24, 6.96–6.92 (3m, 9H, Ar—H), 4.06 (d, 1H, $J = 18.4$, H4′a), 3.73 (d, 1H, $J = 18.4$, H4′b), 3.83 (s, 3H, p-OCH_3), 2.45 (s, 3H, CH_3). 162.45 (C3′), 153.70 (C4), 144.70 (C2), 158.91, 130.53, 130.22, 129.35, 128.75, 127.17, 126.48, 113.72 (12C, Ar—C), 118.52 (C5), 104.14 (CCl_3), 102.64 (C5′), 55.24 (p-OCH_3), 47.35 (C4′), 12.18 (CH_3).
3j	7.87–7.71, 7.52–7.25 (2m, 9H, Ar—H), 4.07 (d, 1H, $J = 18.8$, H4′a), 3.74 (d, 1H, $J = 18.8$, H4′b), 2.46 (s, 3H, CH_3). 162.75 (C3′), 154.08 (C4), 143.80 (C2), 133.35, 132.87, 131.73, 130.14, 129.38, 128.80, 128.55, 126.54 (12C, Ar—C), 120.45 (C5), 104.04 (CCl_3), 102.65 (C5′), 47.38 (C4′), 12.22 (CH_3).
3k	7.2–7.62, 7.57–7.40, 7.24–7.22 (3m, 9H, Ar—H), 4.06 (d, 1H, $J = 18.6$, H4′a), 3.72 (d, 1H, $J = 18.6$, H4′b), 2.44 (s, 3H, CH_3). 163.23 (C3′), 154.43 (C4), 144.45 (C2), 133.91, 131.97, 131.13, 130.63, 130.15, 129.28, 127.01, 121.96 (12C, Ar—C). 121.96 (C5), 104.56 (CCl_3), 103.09 (C5′), 47.89 (C4′), 12.73 (CH_3).

TABLE 4 Selected ^{1}H and ^{13}C MNR Spectral Data of **4**



Compound	*^{1}H NMR ($CDCl_3$/TMS, δ, J (Hz)/^{13}C NMR ($CDCl_3$/TMS, δ)*
4a	7.99–7.85, 7.48–7.27 (2m, 10H, Ar—H), 7.43 (s, 1H, H5), 7.33 (s, 1H, H4′). 159.04 (C4), 152.43 (C3′), 151.13 (C2), 145.36 (C5′), 133.89, 131.39, 129.90, 129.09, 129.02, 128.73, 127.91, 125.95 (12C, Ar—C), 111.34 (C5), 109.04 (C4′), 86.45 (CCl_3).
4b	7.85–7.82, 7.62–7.35, 7.27–7.20 (3m, 9H, Ar—H), 7.40 (s, 1H, H5), 7.27 (s, 1H, H4′), 2.35 (s, 3H, CH_3). 158.96 (C4), 152.63 (C3′), 151.16 (C2), 145.44 (C5′), 138.16, 131.30, 130.74, 129.82, 129.45, 128.87, 128.78, 126.00 (12C, Ar—C), 110.62 (C5), 109.00 (C4′), 86.49 (CCl_3), 21.25 (CH_3).
4c	7.93–7.63, 7.35–7.22, 6.99–6.95 (3m, 9H, Ar—H), 7.44 (s, 1H, H5), 7.31 (s, 1H, H4′), 3.85 (s, 3H, OCH_3). 159.18 (C4), 151.74 (C3′), 150.61 (C2), 144.89 (C5′), 130.12, 128.72, 128.27, 126.86, 126.35, 125.42 (12C. Ar—C), 113.61 (C5), 109.35 (C4′), 108.43 (CCl_3), 54.74 (OCH_3).
4d	8.01–7.86, 7.77–7.61, 7.45–7.24 (3m, 9H, Ar—H), 7.42 (s, 1H, H5), 7.28 (s, 1H, H4′). 159.40 (C4), 151.44 (C3′), 151.39 (C2), 145.52 (C5′), 134.13, 132.50, 130.66, 129.35, 129.00, 128.85, 127.37, 126.10 (12C, Ar—C), 111.67 (C5), 109.27 (C4′), 86.44 (CCl_3).
4e	7.90–7.69, 7.57–7.41 (2m, 9H, Ar—H), 7.68 (s, 1H, H5), 7.38 (s, 1H, H4′). 158.67 (C4), 150.75 (C3′), 150.50 (C2), 144.89 (C5′), 132.53, 131.36, 129.96, 128.99, 128.45, 127.28, 125.54, 121.52 (12C, Ar—C), 112.65 (C5), 108.90 (C4′), 85.87 (CCl_3).
4f	8.46–8.19, 7.90–7.78, 7.44–7.36 (3m, 9H, Ar—H), 7.86 (s, 1H, H5), 7.08 (s, 1H, H4′). 162.17 (C4). 160.50 (C3′), 148.76 (C2), 146.67 (C5′), 152.01, 145.09, 139.81, 131.83, 128.91, 126.94, 125.77, 124.13 (12C, Ar—C), 128.73 (C5), 117.66 (C4′), 105.96 (CCl_3).
4g	7.87–7.76, 7.67–7.55, 7.44–7.34 (3m, 10H, Ar—H), 7.24 (s, 1H, H4′), 2.63 (s, 3H, CH_3). 154.78 (C4), 151.10 (C3′), 147.95 (C2), 145.58 (C5′), 137.82 (C5), 134.62, 132.15, 130.28, 129.13, 128.81, 128.32, 126.01, 116.67 (12C, Ar—C), 108.52 (C4′), 86.47 (CCl_3), 12.80 (CH_3).
4h	7.86–7.81, 7.68–7.52, 7.44–7.22 (3m, 9H, Ar—H), 7.25 (s, 1H, H4′), 2.58 (s, 3H, CH_3), 2.37 (s, 3H, *p*-CH_3). 154.55 (C4), 150.91 (C3′), 147.88 (C2), 145.39 (C5′), 137.45 (C5), 131.76, 130.88, 129.05, 128.82, 128.32, 128.17, 127.51, 125.96 (12C, Ar—C), 108.43 (C4′), 86.42 (CCl_3), 21.22 (*p*-CH_3), 12.73 (CH_3).
4i	7.89–7.70, 7.45–7.23, 7.01–6.97 (3m, 9H, Ar—H), 7.25 (s, 1H, H4′), 3.86 (s, 3H, *p*-OCH_3), 2.62 (s, 3H, CH_3). 155.21(C4), 154.68 (C3′), (C2) , (C5′), (C5), 133.01, 130.76, 128.57, 127.94, 127.43, 127.05, 126.25, 126.04 (12C, Ar—C), 108.50 (C4′), 86.34 (CCl_3), 56.19 (*p*-OCH_3, 12.63 (CH_3).
4j	7.87–7.84, 7.73–7.57, 7.49–7.39 (3m, 9H, Ar—H), 7.24 (s, 1H, H4′), 2.61 (s, 3H, CH_3), 157.08 (C4), 151.17 (C3′), 146.72 (C2), 145.50 (C5′), 137.71 (C5), 133.54, 130.13, 129.56, 129.19, 128.45, 126.17, 125.99, 116.76 (12C, Ar—C), 108.69 (C4′), 86.42 (CCl_3), 12.78 (CH_3).
4k	7.86–7.83, 7.67–7.54, 7.44–7.41 (3m, 9H, Ar—H), 7.24 (s, 1H, H4′), 2.61 (s, 3H, CH_3). 157.05 (C4), 151.19 (C3′), 146.74 (C2), 145.51 (C5′), 137.73 (C5), 133.56, 132.18, 130.87, 129.73, 129.47, 126.00, 121.78, 116.77 (12C, Ar—C), 108.71 (C4′), 86.43 (CCl_3), 12.78 (CH_3).

and convenient procedure to obtain trichloromethylated 2-[4,5-dihydro-1*H*-pyrazol-1-yl]-4-aryl-5-alkylthiazoles (**3a–k**) and the respective bis-aromatic 2-[1*H*-pyrazol-1-yl]-4-aryl-5-alkylthiazoles (**4a–k**).

EXPERIMENTAL

Unless otherwise indicated all common reagents and solvents were used as obtained from commercial suppliers without further purification. All melting points were determined on a Reichert Thermovar apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker DPX 400 spectrometer (^{1}H at 400.13 MHz and ^{13}C at 100.62 MHz), 5-mm sample tubes, 298 K, digital resolution ±0.01 ppm, in $CDCl_3$ and using TMS as internal reference. The CHN elemental analyses were performed on a Perkin-Elmer 2400 CHN elemental analyzer.

*Preparation of 2-(3-Phenyl-5-hydroxy-5-trichloromethyl-4,5-dihydro-1*H *-pyrazol-1-yl)-4-aryl-5-alkylthiazoles (***3a–k***)*

General Procedure. In a 50-ml flask a mixture of 1.70 g (5 mmol) **1** and 5 mmol **2**, in 20 ml of ethanol, was magnetically stirred and warmed for 24 h at 70°C. After cooling (10–15°C), the crystalline solids **3** were filtered off and washed with cold ethanol (10 ml). Products **3** were obtained in good purity by evaporating the residual solvent in vacuum. Yields and elemental analyses are listed in Table 1.

*Preparation of 2-(3-Phenyl-5-trichloromethyl-1*H*-pyrazol-1-yl)-4-aryl-5-alkylthiazoles (***4a–k***)*

General Procedure. In a 50-ml flask a mixture of 3 mmol of **3**, 2.5 ml of sulfuric acid, and 20 ml of chloroform was magnetically stirred at reflux for 24 h. To this mixture was added slowly 5 ml of ice water. A saturated solution of sodium hydroxide was added to the initial solution at room temperature until pH ≈7–8. The resulting solution was extracted with chloroform (3 × 10 ml). The combined organic layers were dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure. Products **4** were obtained in good purity by evaporation of the residual solvent in vacuum. Yields and elemental analyses are listed in Table 3.

REFERENCES

[1] Welch, J. T. Tetrahedron 1987, 43, 3123.
[2] Schetinger, M. R. C.; Porto, N. M.; Moretto, M. B.; Morsch, V. M.; Rocha, J. B. T.; Vieira, V.; Moro, F.; Neis, R. T.; Bittencourt, S.; Bonacorso, H. G.; Zanatta, N. Neurochem Res 2000, 25, 919.
[3] Rubin, M. A.; Albach, C. A.; Berlese, D. B.; Bonacorso, H. G.; Bittencourt, S. R. T.; Queiroz, C. M. T.; Maixner, A. E.; Mello, C. F. Braz J Med Biol Res 2000, 33, 1069.
[4] Souza, F. R.; Fighera, M. R.; Lima, T. T. F.; Bastiani, J.; Barcellos, I. B.; Almeida, C. E.; Oliveira, M. R.; Bonacorso, H. G.; Flores, A. E.; Mello, C. F. Pharmacol, Biochem Behav 2000, 68, 525.
[5] Sielecki, T. M.; Boylan, J. F.; Benfield, P. A.; Trainor, G. L. J Med Chem 2000, 43, 1.
[6] Martins, M. A. P.; Siqueira, G. M.; Bastos, G. P.; Bonacorso, H. G.; Zanatta, N. J Heterocycl Chem 1996, 33, 1619.
[7] Spiegler, W.; Götz, N. Synthesis 1986, 69.
[8] Zanatta, N.; Barichello, R.; Bonacorso, H. G.; Martins, M. A. P. Synthesis 1999, 765.
[9] Bonacorso, H. G.; Bittencourt, S. T.; Wastowski, A. D.; Wentz, A. P.; Zanatta, N.; Martins, M. A. P. Tetrahedron Lett 1996, 37, 9155.
[10] Martins, M. A. P.; Flores, A. F. C.; Bastos, G. P.; Sinhorin, A.; Bonacorso, H. G.; Zanatta, N. Tetrahedron Lett 2000, 41, 293.
[11] Martins, M. A. P.; Freitag, R. A.; Rosa, A.; Flores, A. F. C.; Zanatta, N.; Bonacorso, H. G. J Heterocycl Chem 1999, 36, 217.
[12] Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V. Comprehensive Heterocyclic Chemistry II; Elsevier: New York, 1996; Vol. 3.
[13] Lednicer, D.; Mitscher, L. A. Organic Chemistry of Drugs Synthesis; Wiley: New York, 1977; Vols. 1–3.
[14] De Arriba, A. F.; Gómez-Casajús, L. A.; Cavalcanti, F.; Almansa, C.; García-Rafanell, J.; Forn, J. Eur J Pharmacol 1996, 318, 341.
[15] De Arriba, A. F.; Gómez-Casajús, L. A.; Cavalcanti, F.; Almansa, C.; García-Rafanell, J.; Forn, J. J Med Chem 1997, 40, 547.
[16] Harper, R. W.; Jackson, W. T.; Froelich, L. L.; Boyd, R. J.; Aldridge, T. E.; Herron, D. K. J Med Chem 1994, 37, 2411.
[17] Ishii, S.; Yagi, K.; Umehara, T.; Kudo, M.; Nawamaki, T.; Watanabe, S. Jpn Kokai Tokkyo Koho JP 02, 129,171 [90,129, 171], May 17, 1990; Chem Abstr 1990, 113, 172014a.
[18] Buntain, I. G.; Hatton, L. R.; Hawkins, D. W.; Pearson, C. J.; Roberts, D. A. Eur Patent Application EP 295, 117, Dec. 14, 1988; Chem Abstr 1990, 112, 35845n.
[19] Sing, S. P.; Kumar, D.; Kapoor, J. K. J Chem Res, Synrop 1993, 163.
[20] Peet, N. P.; Sunder, S.; Barbuch, R. J.; Whalon, M. R. J Heterocycl Chem 1988, 25, 543.
[21] Singh, S. P.; Kumar, D.; Jones, B. G.; Threadgill, M. D. J Fluorine Chem 1999, 94, 1999.
[22] Rezessy, B.; Zubovics, Z.; Kovács, J.; Tóth, G. Tetrahedron 1999, 55, 5909.
[23] Saloutina, L. V.; Zapevalov, A. Ya.; Kodess, M. I.; Saloutin, V. I.; Aleksandrov, G. G.; Chupakhin, O. N. J Fluorine Chem 2000, 104, 155.
[24] Bonacorso, H. G.; Oliveira, M. R.; Wentz, A. P.; Wastowski, A. D.; Oliveira, A. B.; Hörner, M.; Zanatta, N.; Martins, M. A. P. Tetrahedron 1999, 55, 345.
[25] Martins, M. A. P.; Sinhorin, A. P.; Zimmermann, N. E. K.; Zanatta, N.; Bonacorso, H. G.; Bastos, G. P. Synthesis 2001, 1959.
[26] Martins, M. A. P.; Colla, A.; Clar, G.; Fischer, P.; Krimmer, S. Synthesis 1991, 483.
[27] Martins, M. A. P.; Siqueira, G. M.; Bastos, G. P.; Bonacorso, H. G.; Zanatta, N. J Heterocycl Chem 1996, 33, 1619.
[28] Zanatta, N.; Pacholski, I. L.; Faoro, D.; Bonacorso, H. G.; Martins, M. A. P. Synthetic Commun 2001, 31, 2855.
[29] Zanatta, N.; Pacholski, I. L.; Blanco, I.; Martins, M. A. P. J Braz Chem Soc 1991, 2, 118.
[30] Zanatta, N.; Cortelini, M. F. C.; Carpes, M. J. S.; Bonacorso, H. G.; Martins, M. A. P. J Heterocycl Chem 1997, 34, 509.
[31] Bonacorso, H. G.; Bittencourt, S. R. T.; Wastowski, A. D.; Wentz, A. P.; Zanatta, N.; Martins, M. A. P. J Heterocycl Chem 1999, 36, 45.
[32] Bonacorso, H. G.; Wastowski, A. D.; Zanatta, N.; Martins, M. A. P.; Naue, J. A. J Fluorine Chem 1998, 92, 23.
[33] Eicher, T.; Tietze, L. F. Reaktionen und Synthesen; George Thieme Verlag: Stuttgart, Germany, 1981.