Bioorganic & Medicinal Chemistry Letters 20 (2010) 6920–6924

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Pyrazole derivatives from azines of substituted phenacyl aryl/cyclohexyl sulfides and their antimycobacterial activity

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ARTICLE INFO

Article history:
Received 6 July 2010
Revised 14 September 2010
Accepted 29 September 2010
Available online 7 October 2010

Keywords:
ω-Substituted acetophenone azines
Vilsmeier's reagent
Pyrazole derivatives
Microwave irradiation
Antimycobacterial activity

ABSTRACT

Azines derived from substituted phenacyl aryl/cyclohexyl sulfide on treatment with excess phosphorous oxychloride in *N*,*N*-dimethylformamide have been found to yield two isomeric pyrazoles in each case. A plausible mechanism has been suggested for the formation of the products. The antimycobacterial activity of the isomeric compounds has been tested against *Mycobacterium tuberculosis* (MTB).

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Tuberculosis is a chronic infectious disease that is transmitted by cough-propelled droplets that carry the etiologic bacterium, *Mycobacterium tuberculosis*. Although currently available drugs kill most isolates of *M. tuberculosis*, strains resistant to each of these have emerged, and multiply resistant strains are increasingly widespread. The growing problem of drug resistance combined with a global incidence of several thousands of new cases per year underscore the urgent need for new antituberculosis therapies.[1] In this connection, several pyrazole derivatives have been tested for their antitubercular activity. For example, a series of 5-*tert*-butyl-*N*-pyrazol-4-yl-4,5,6,7-tetrahydrobenzo[*d*]isoxazole-3-carboxamide derivatives have been shown to be novel potent *M. tuberculosis* PS inhibitors.[2] Another series of 5-aryl-1-isonicotinoyl-3-(pyridin-2-yl)-4,5-dihydro-1*H*-pyrazole derivatives exhibited an interesting in vitro antimycobacterial activity against *M. tuberculosis*, their MIC values ranging from 8 to 16 μg/ml.[3] Similarly 1-acetyl-3,5-diphenyl-4,5-dihydro-(1*H*)-pyrazole derivatives were screened against *M. tuberculosis* strain $H_{37}Rv$.[4] Hydrazone products, ethyl 2-[(3,5-dimethylpyrazole-4-yl)hydrazono]-3-oxobutyrate and methyl 2-[(3,5-dimethylpyrazole-4-yl)hydrazono]-4-methoxy-3-oxobutyrate showed 29 and 28% inhibition against *M. tuberculosis* $H_{37}Rv$, respectively.[5] Pyrazolone derivatives bearing a 4-substituted benzyl moiety at N2 were found to be more active, even if they resulted to be less active than the pyrazole series.[6] Structure–activity relationship studies revealed that the presence of the *p*-chlorobenzoyl moiety at the C4 of the pyrazole ring is fundamental for the antimycobacterial activity of some of the pyrazole compounds.[7] 1-(3,5-Diaryl-4,5-dihydro-1*H*-pyrazol-4-yl)-1*H*-imidazole were tested against a strain of *M. tuberculosis* $H_{37}Rv$ and showed a good antimycobacterial activity reaching MIC values of 4 μg/mL for six compounds of the series.[8] Substituted 1-(2-hydroxybenzoyl)-3-methyl-1*H*-pyrazol-5(4*H*)-one has shown promising antitubercular activity.[9]

Realizing the importance of pyrazole nucleus in the antimycobacterial studies, it is planned to synthesize arylthio/cyclohexylthio substituted pyrazoles and test their activity and the results are described in this Letter.

Substituted phenacyl aryl/cyclohexyl sulfides **1** have been prepared[10–17] by the reaction of substituted phenacyl bromide with cyclohexane thiol or benzene thiol. Symmetrical ω-aryl/cyclohexylthio substituted acetophenone azines **2** were prepared, which are all new to the best our knowledge, in quantitative yield by the reaction of ω-arylthioacetophenone and hydrazine sulfate in presence of sodium acetate in ethanol under reflux. The reaction of ω-arylthio substituted acetophenone azines **2** with Vilsmeier's reagent (taken in excess, 1:8 ratio of substrate to reagent) took place smoothly with quantitative conversion of the starting material (Scheme 1).[18] In all the cases investigated, one product, **3**, was obtained as the major product with more than 80% yield in many cases. Another compound **4** is obtained in poor yield in many cases, though from **2h** and **2i**, this compound is obtained as the major

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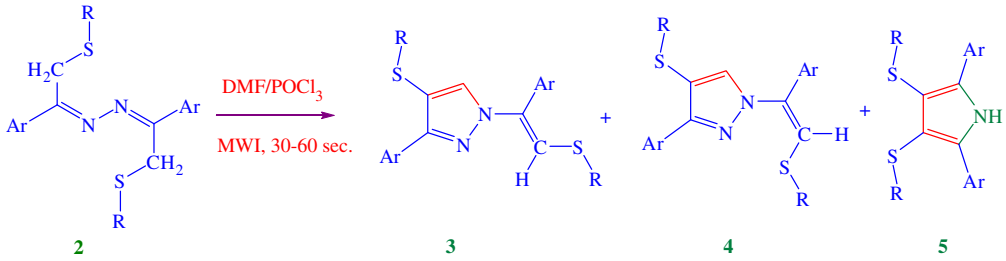
doi:10.1016/j.bmcl.2010.09.137



	Ar	R
a	C_6H_5	*p*-ClC_6H_4
b	*p*-$CH_3C_6H_4$	*p*-ClC_6H_4
c	*p*-$OCH_3C_6H_4$	*p*-ClC_6H_4
d	*p*-ClC_6H_4	*p*-ClC_6H_4
e	2-Naphthyl	*p*-ClC_6H_4
f	*p*-ClC_6H_4	*p*-$CH_3C_6H_4$
g	*p*-ClC_6H_4	C_6H_5
h	C_6H_5	C_6H_{11}
i	*p*-$CH_3C_6H_4$	C_6H_{11}
j	*p*-$OCH_3C_6H_4$	C_6H_{11}
k	*p*-ClC_6H_4	C_6H_{11}
l	*p*-$NO_2C_6H_4$	C_6H_{11}

Scheme 1. Synthesis of pyrazoles and pyrroles.

product (Table 1). In a few cases (**2a**, **2b, 2d, 2i**, and **2k**), apart from **3** and **4**, a third product **5** was also obtained in small amount. All the compounds were column separated and fully characterized by NMR spectral data.

The ^{1}H NMR spectrum of **3d**[19] has two singlets appearing at 7.25 and 7.44 ppm accounting for one hydrogen each. There are four doublets each accounting for two hydrogens and a multiplet accounting for eight hydrogens suggesting the presence four aryl rings. Out of the 21 carbon signals noticed in the ^{13}C NMR spectrum of **3d**, eleven of them are quaternary, the remaining being methine carbons. The spectral data clearly suggest that a pyrazole ring has been formed at one end of the azine system with the generation of a vinyl unit at the other. The signal at 7.44 ppm gives a strong contour with the carbon at 153.0 ppm in the HMBC spectrum, indicating that this hydrogen to be the ring hydrogen of the pyrazole. The other olefinic hydrogen gives HMBC contours

Table 1
Yield, physical constants, and anti-TB activities of pyrazole derivatives

Entry	Ar	R	Yield (%)		Mp (°C)		MIC (μg/ml)	
			3	**4**	**3**	**4**	**3**	**4**
a	C_6H_5	*p*-ClC_6H_4	86	9	118–119	—[b]	12.5	>25
b	*p*-$CH_3C_6H_4$	*p*-ClC_6H_4	83	8	—[b]	—[b]	6.25	12.5
c	*p*-$OCH_3C_6H_4$	*p*-ClC_6H_4	82	—[a]	—[b]		6.25	—[c]
d	*p*-ClC_6H_4	*p*-ClC_6H_4	86	10	128–129	—[b]	1.56	3.13
e	2-Naphthyl	*p*-ClC_6H_4	81	15	133–134	—[b]	6.25	12.5
f	*p*-ClC_6H_4	*p*-$CH_3C_6H_4$	84	—[a]	—[b]		12.5	—[c]
g	*p*-ClC_6H_4	C_6H_5	82	7	—[b]	—[b]	25.0	>25.0
h	C_6H_5	C_6H_{11}	38	60	90–91	—[b]	6.25	12.5
i	*p*-$CH_3C_6H_4$	C_6H_{11}	42	50	93–94	107–108	3.13	6.25
j	*p*-$OCH_3C_6H_4$	C_6H_{11}	73	25	—[b]	—[b]	3.13	12.5
k	*p*-ClC_6H_4	C_6H_{11}	78	—[a]	97–98		1.56	—[c]
l	*p*-$NO_2C_6H_4$	C_6H_{11}	75	20	129–131	—[b]	0.78	1.56
Isoniazid							0.05	
Ethambutol							1.56	
Pyrazinamide							6.25	

[a] Not isolated.
[b] Viscous liquid.
[c] Not tested.

with the carbons at 134.7 and 135.4 ppm, suggesting these carbons to be the *ipso* carbons of the *p*-chlorophenyl ring. From the single crystal X-ray analyses[20,21] of compounds **3a** and **3h**, it is found that the pyrazolyl ring and the olefinic hydrogens are *cis* to each other (Figs. 1 and 2).

The ^{1}H NMR spectrum of **4b**[22] shows two singlets at 6.49 and 7.70 ppm. This is in difference to **3**, where there are two singlets at 7.25 and 7.44 ppm. All other hydrogens and carbons are having almost same pattern. This clearly shows that **3** and **4** are geometrical isomers, with **4** having a *Z* form.

In some cases (**2a, 2b, 2d**, **2i**, and **2k**), small amount of another compound **5** has also been isolated from the reaction mixture. This compound is found to be a symmetrical system, with well defined simple NMR spectrum. For **5d**,[23] four pairs of doublets accounting for sixteen hydrogens and one hydrogen which is replaceable by D_2O are there in its ^{1}H NMR spectrum. This indicates that the compound **5d** has a NH. The ^{13}C NMR and DEPT spectra also account for two identical pairs of aryl, four aryl in total and signals for two quaternary carbons. The structure can be easily arrived at to be 2,3,4,5-tetra substituted symmetrical pyrrole.

The tentative mechanism of the reaction for the formation **3** and **4** are given in Scheme 2. It should be noticed that even in the presence of excess Vilsmeier's reagent, only monoformylation occurs, either giving **3** or **4** as there is no scope for further formylation. This is contrast with the results of a similar reaction carried out on acetophenone azines, where further formylation has occurred giving

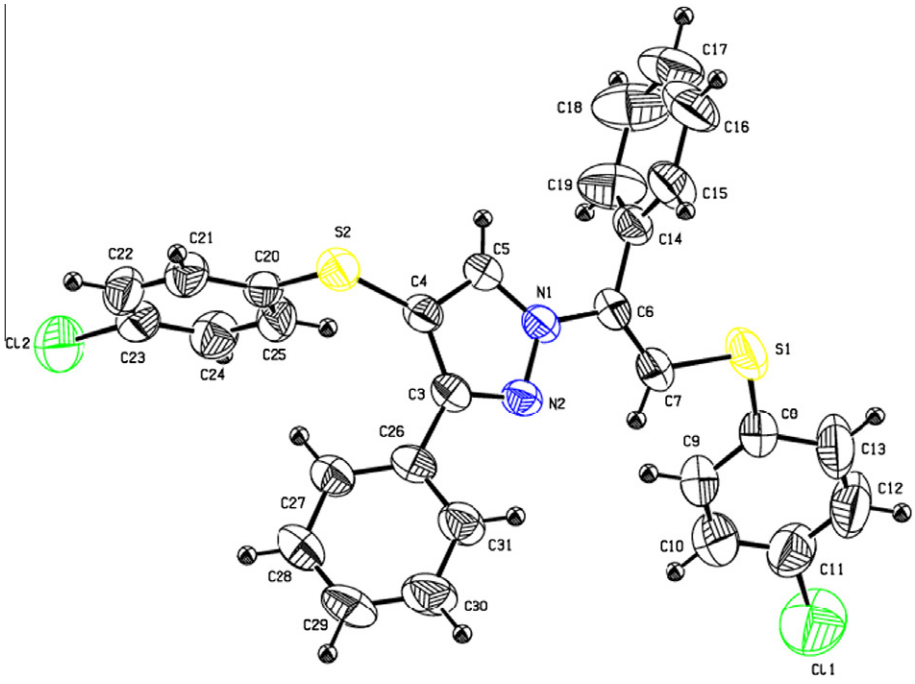


Figure 1. ORTEP diagram of compound **3a**.

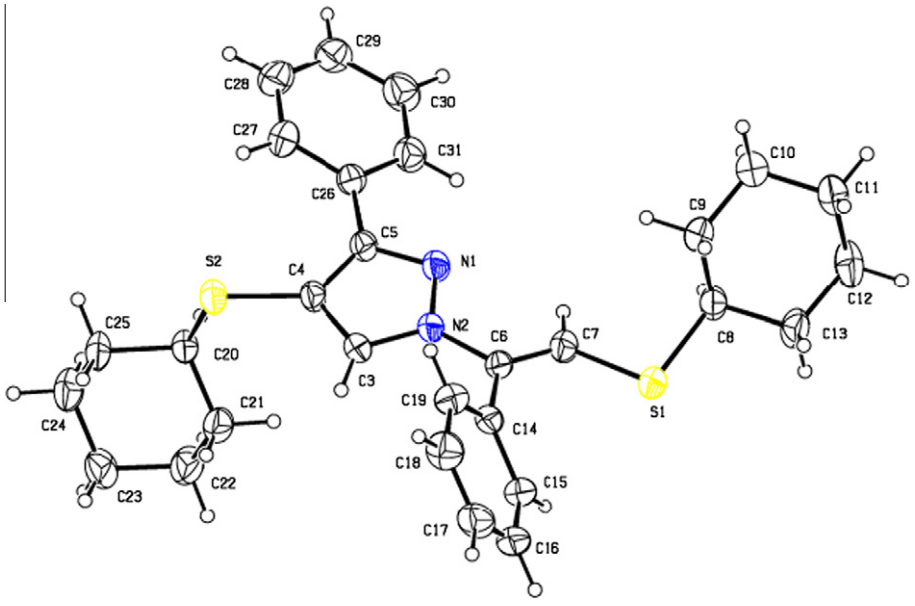
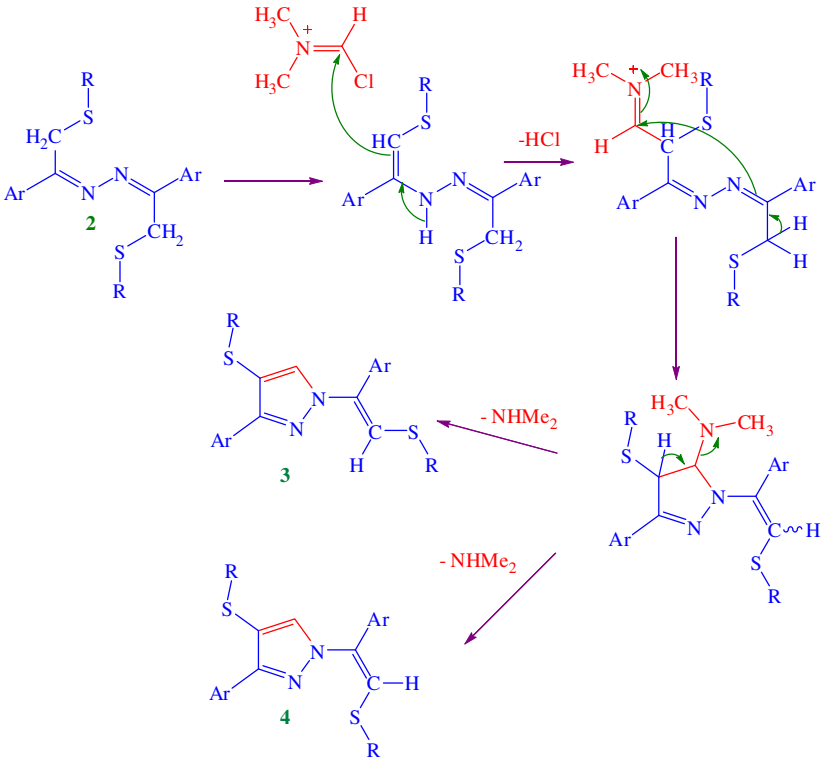
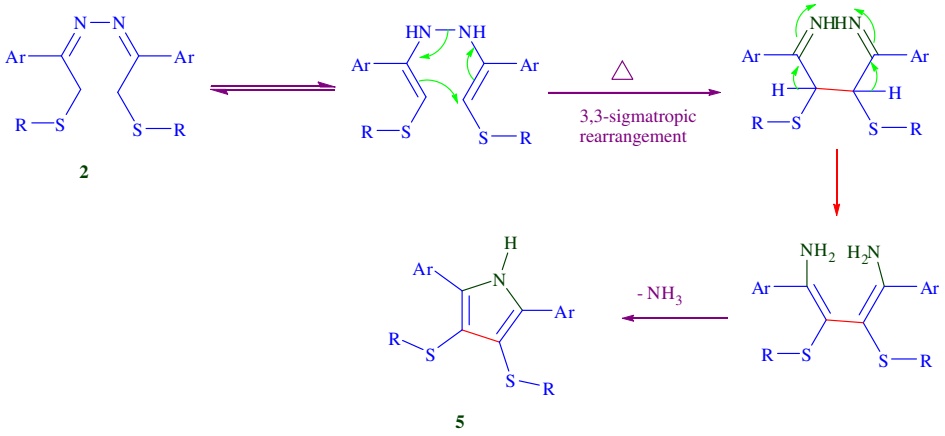


Figure 2. ORTEP diagram of compound **3h**.



Scheme 2. Possible mechanism for the formation of compounds **3** and **4**.



Scheme 3. Mechanism for the formation of compound **5** (Piloty pyrrole synthesis).

different types of products.[24] The stability of **3** over **4** may be the reason for the higher yield of **3** in the reaction mixture. This is also confirmed by molecular modeling, optimized using PM3 (semi-empirical method) in Arguslab 4.0.1, where the *E* conformer was found to be stable by 11 KJ/mol.

Compound **5** obtained in some cases can be explained by the popular Piloty pyrrole synthesis. Before the Vilsmeier's reagent attacks the azine, the system would have undergone rearrangement by the Lewis acid character of phosphorous oxychloride and the mechanism for the formation of **5** is given in Scheme 3.

The antimycobacterial activity of the isomeric pyrazoles (**3/4**) has been screened for their in vitro activity against *M. tuberculosis* H37Rv (MTB) by agar dilution method for the determination of MIC in triplicates. The MIC values of **3/4** along with the standard drugs for comparison are provided in Table 1. The isomer **3** seems to be more active than **4** in all the cases, the activity being doubled in many cases. In general, the cyclohexylthio substituted pyrazoles (**h–l**) are more active than the arylthio substituted systems (**a–g**) in the respective series. Excellent activity has been noticed when a *p*-nitrophenylthio ring (**3l** and **4l**) is there in the pyrazole ring. **3d** and **3k** are as active as ethambutol. The antimycobacterial activity is remarkable when all the aryl rings carry *p*-chloro group (**3d**) or when the substituents are *p*-chlorophenylthio and cyclohexylthio groups (**3k**). It has already been reported that a *p*-chlorobenzoyl moiety at the C4 of the pyrazole ring has found to have remarkable antimycobacterial activity in some of the pyrazole compounds.[7] As observed earlier,[9] in our case also, some of the 1-substituted pyrazoles (**3/4**) are found to be antitubercular active.

Acknowledgments

The authors thank Department of Science and Technology, New Delhi for assistance for the NMR spectrometer facility. Financial

support from Madurai Kamaraj University, Madurai for one of the authors (R.M.) is gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.09.137.

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18. *General procedure for the synthesis of pyrazole derivatives* ***3*** *and* ***4*** *and pyrrole derivative* ***5***: To a mixture of 1-aryl-2-(aryl/cyclohexylsulfanyl)-1-ethanone *N*-[(*Z*)-1-aryl-2-(aryl/cyclohexylsulfanyl)ethylidene]hydrazones **2** (0.003 mol) and 3 mL of dimethyl formamide kept in ice bath at 0 °C, phosphorous oxychloride (0.024 mol) was added dropwise for 5–10 min. The reaction mixture was then irradiated under microwaves for 30–60 s. The process of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into crushed ice and extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate. The different compounds present in the mixture, **3**, **4** and **5** were separated by column chromatography using petroleum ether and ethyl acetate mixture as eluent.
19. *3-(4-Chlorophenyl)-1-(E)-1-(4-chlorophenyl)-2-[(4-chlorophenyl)sulfanyl]-1-ethenyl-4-[(4-chlorophenyl)sulfanyl]-1H-pyrazole* (Table 1, entry **3d**): colourless crystal (dichloromethane), yield 86%, mp 128–129 °C, time 30 s; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.97 (d, J = 8.7 Hz, 2H), 7.16 (d, J = 8.7 Hz, 2H), 7.25 (s, 1H), 7.31–7.44 (m, 9H), 7.49 (d, J = 8.7 Hz, 2H), 7.92 (d, J = 8.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 106.3, 117.1, 127.2, 128.6, 128.8, 129.1, 129.4, 129.5, 130.0, 130.7, 130.8, 131.0, 131.4, 133.3, 133.4, 134.7, 135.4, 136.0, 136.2, 136.3, 153.0. Anal. Calcd for $C_{29}H_{18}Cl_4N_2S_2$: C, 58.01; H, 3.02; N, 4.67. Found: C, 58.09; H, 3.08; N, 4.73.
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22. *4-[(4-Chlorophenyl)sulfanyl]-1-[(Z)-2-[(4-chlorophenyl)sulfanyl]-1-(4-methyl phenyl)-1-ethenyl]-3-(4-methylphenyl)-1H-pyrazole* (Table 1, entry **4b**): viscous liquid, yield 8%, time 30 s; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.36 (s, 3H), 2.38 (s, 3H), 6.49 (s, 1H), 7.05 (d, J = 8.4 Hz, 2H), 7.16–7.26 (m, 8H), 7.34 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 7.70 (s, 1H), 7.96 (d, J = 8.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.2, 21.3, 105.5, 114.0, 127.1, 127.2, 127.4, 128.9, 129.0, 129.1, 129.4, 129.6, 131.0, 131.8, 132.6, 133.7, 134.9, 135.4, 137.0, 137.5, 138.4, 139.3, 153.2.
23. *2,5-Bis(4-chlorophenyl)-3,4-bis[(4-chlorophenyl)sulfanyl]-1H-pyrrole* (**5d**): colourless crystal (ethyl acetate), yield 3%, mp 112–113 °C, time 30 s; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.95 (d, J = 8.7 Hz, 4H), 7.06 (d, J = 8.7 Hz, 4H), 7.40 (d, J = 8.1 Hz, 4H), 7.63 (d, J = 8.1 Hz, 4H), 9.00 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 114.2, 127.4, 128.3, 128.8, 129.2*, 131.0, 134.4, 136.5, 136.8 (* one carbon merged with other). Anal. Calcd for $C_{28}H_{17}Cl_4NS_2$: C, 58.65; H, 2.99; N, 2.44. Found: C, 58.75; H, 3.12; N, 2.52.
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