Temperature-Dependent Product Selectivity in the *Vilsmeier–Haack* Reaction on Bis(phenylhydrazones) of Bis(aroylmethyl) Sulfides (=1,1′-[Thiobis(methylene)]bis[arylmethanone] Bis(2-phenylhydrazones)): Synthesis of 3-Aroylindoles (=Aryl(1*H*-indol-3-yl)methanones)

by **Nidhin Paul** and **Shanmugam Muthusubramanian***

Department of Organic Chemistry, School of Chemistry, Madurai Kamaraj University, Madurai-625021, Tamil Nadu, India
(phone/fax: +91-452-2459845; e-mail: muthumanian2001@yahoo.com)

The bis(phenylhydrazone) of substituted diphenacyl sulfides (=1,1′-[thiobis(methylene)]bis[arylmethanone] bis(2-phenylhydrazones)) **1** underwent a tandem sequence of reactions upon treatment with *Vilsmeier* reagent, ultimately yielding 3-aroylindoles (=aryl(1*H*-indol-3-yl)methanones) **3** (*Scheme 1* and *Table 1*). The reaction seems to be product selective depending upon the reaction temperature.

Introduction. – Since its discovery in 1927, the *Vilsmeier* (or *Vilsmeier–Haack*) reaction has been developed into a powerful synthetic tool, and it continues to attract considerable attention [1]. Even though initially used for the introduction of a formyl group in activated aromatic and heteroaromatic compounds, this reaction has also found increasing application in formylating active methylene groups.

Results and Discussion. – In a recent publication, we have explored the possibility of using the *Vilsmeier–Haack* reaction in preparing different benzo[*b*]thiophenes [2] from diphenacyl sulfides (=1,1′-[thiobis(methylene)]bis[phenylmethanones]). With this background, we now applied the *Vilsmeier* reaction to bis(phenylhydrazone) **1** of diphenacyl sulfides (*Scheme 1*) with the expectation of getting S-linked bis[1*H*-pyrazoles] **2**. The starting materials were prepared by a known procedure [3]. Then, to an ice-cold solution of bis(phenylhydrazone) **1** in DMF, $POCl_3$ was added, and after 30 min, the temperature was raised to 80° and kept at that temperature for 2 h (*Scheme 1*). On completion of the reaction, 3-substituted indoles, *i.e.*, aryl (1*H*-indol-3-yl)methanones **3**, and 1,3-diaryl-1*H*-pyrazole-4-carboxaldehydes **4** were obtained as the products (*Table 1*). It was noticed that the temperature has a prominent effect on the product selectivity. The formation of **3** was observed at higher temperature. On keeping the reaction mixture for 24 h at room temperature without increasing the temperature, only **4** was obtained (*Table 1*). The formation of 1*H*-pyrazolecarboxaldehydes **4** by the *Vilsmeier–Haack* reaction of simple acetophenone arylhydrazones has already been reported [4].

A mechanism for the formation of the 3-aroylindoles **3** and pyrazoles **4** from **1** is proposed in *Scheme 2*. Monoformylation of **1a** leads to compound **5** with concomitant removal of the S-compound **6**. Phenylhydrazone **5** rearranges to aminoaldehyde **7**

Scheme 1. *Synthesis of 3-Aroylindoles* **3** *and Pyrazoles* **4**. For R, see *Table 1.*

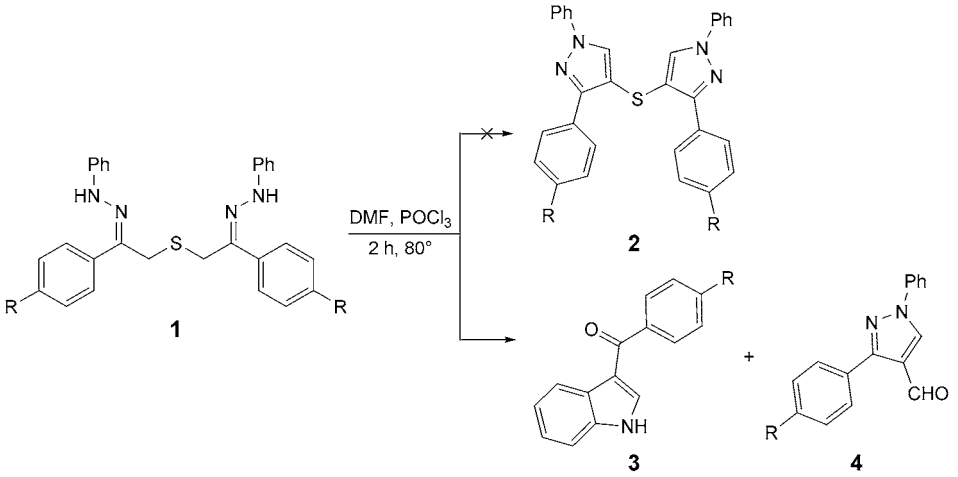


Table 1. *Yield of* **3** *and* **4** *at Different Temperatures*

	R	Yield [%][a]) (80–83°)		Yield [%][b]) (59–63°)		Yield [%][b]) (25°)	
		3	**4**	**3**	**4**	**3**	**4**
a	H	74	12	44	41	0	77
b	Me	75	15	40	48	0	81
c	Cl	78	9	37	49	0	68
d	Br	77	14	42	43	0	72
e	MeO	79	10	41	45	0	79
f	Ph	73	15	39	44	0	75

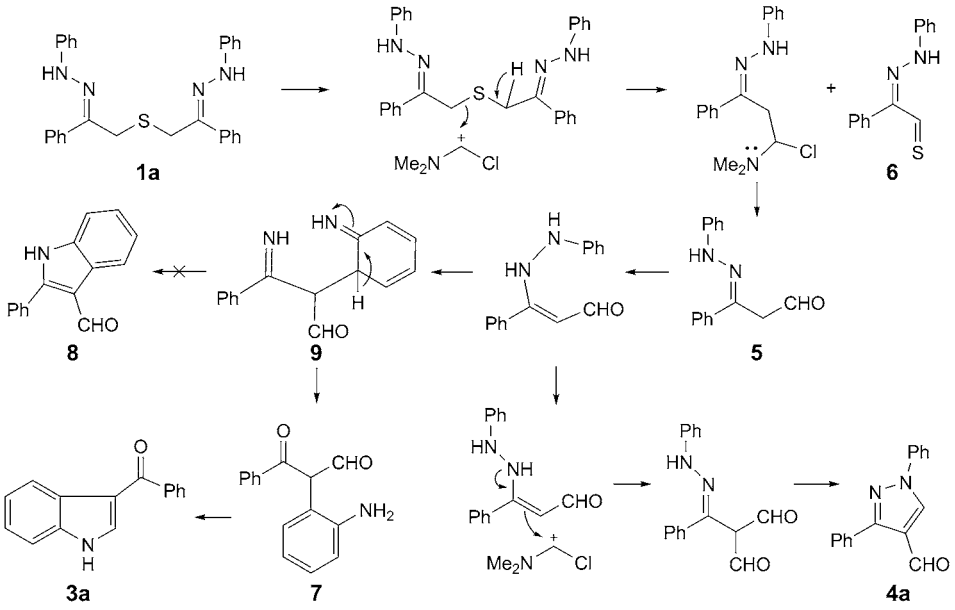
[a]) Yield after purification by column chromatography. [b]) Yield determined by ^{1}H-NMR spectroscopy of the crude product mixture.

which, on further tautomerization and condensation, yields **3a**. The expected *Fischer* indole cyclization of **5** does not occur. The second formylation of phenylhydrazone **5** results in pyrazole-4-carboxaldehyde **4a**.

When the reaction was conducted at higher temperature, before the second formylation takes place on **5**, enolization followed by the 3,3-sigmatropic rearrangement occurs resulting in **7**. Again **5** could have undergone a *Fischer* indole-type reaction to give indole **8**, but once **9** is formed, the enolization is preferred at the formyl rather than at the C=NH group, thus leading the cyclization the other way. The formation of the oxothial corresponding to **6** from diphenacyl sulfide has been proposed in a different reaction studied by us [5].

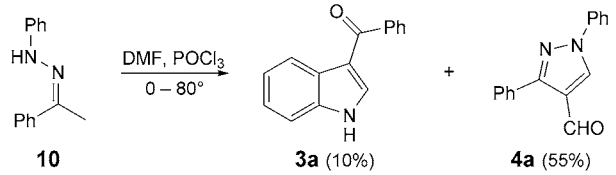
Acetophenone phenylhydrazone can also act as precursor for 3-benzoylindole **3a** by the mechanism shown in *Scheme 2*. However, indoles **3** have not been isolated earlier from this source [4]. To ascertain this fact, in a separate experiment, the *Vilsmeier–Haack* reaction of simple acetophenone phenylhydrazone **10** was conducted

Scheme 2. *Mechanism of Formation of 3-Aroylindoles* **3** *and Pyrazole* **4**



with a slight variation from the reported procedure [4], *i.e.*, **10** was subjected to the *Vilsmeier* reaction as described for **1**. NMR Analysis of the crude product revealed the formation of 55% of 1*H*-pyrazole-4-carbaldehyde **4a** along with 10% of 3-benzoylindole **3a** (*Scheme 3*).

Scheme 3. *Formation of 3-Benzoylindole* **3a** *from* **10**



The structure of indole **3c** (R = Cl) was confirmed by NMR, mass, and crystal analysis and was in agreement with the reported values [6]. In the ^{1}H-NMR spectrum of **3c**, the NH group appears as a broad *s* at δ(H) 12.12 and H–C(2) as another broad *s* at δ(H) 7.96. In the ^{13}C-NMR spectrum, the C-atom of the C=O group resonates at δ(C) 188.2. The complete assignment of the ^{1}H- and ^{13}C-NMR signals along with the HMBC data are shown in *Fig. 1*. The mass spectrum of **3a** (*m*/*z* 220.0768, $[M-1]^+$; calc. 220.0841) was also in agreement with the proposed structure. The structure of the 3-aroylindoles **3** was finally confirmed by a single-crystal X-ray analysis of **3c** (*Fig. 2*). In the NMR spectra of 1*H*-pyrazole-4-carboxaldehyde **4e**, the formyl H-atom appears as a *s* at δ(H) 10.02 and the formyl C-atom at δ(C) 185.1; the H-atom of the pyrazole ring gives rise to a *s* at δ(H) 8.51.

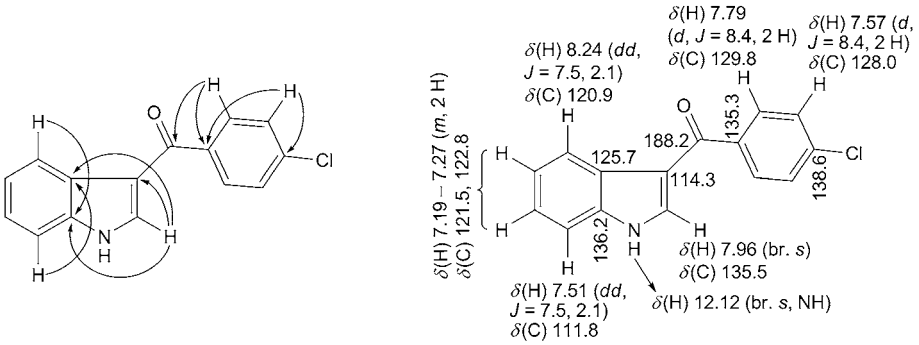


Fig. 1. *HMBCs* (H → C) *and NMR data of* **3c**

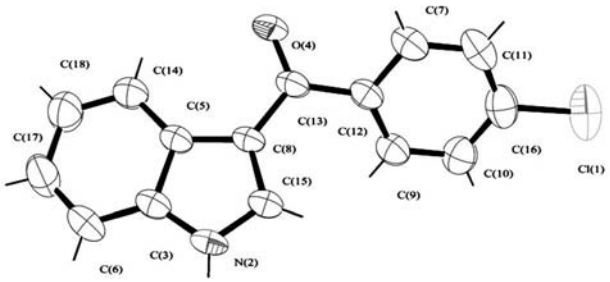


Fig. 2. *ORTEP Diagram of* **3c**. Arbitrary atom numbering.

Conclusions. – We optimized a method for the preparation of 3-aroylindoles (= aryl(1*H*-indol-3-yl)methanones) through an unusual *Vilsmeier–Haack* pathway. The remarkable product selectivity based on the reaction temperature is worth mentioning.

The authors thank *DST*, New Delhi, for funds under the *IRHPA* program towards high-resolution NMR spectroscopy. Dr. *N. Srinivasan*, Thiagarajar College, Madurai, India, and Prof. *J. C. Menéndez*, Departamento de Química Orgánica y Farmacéutica, Universidad Complutense de Madrid, Spain, are acknowledged for the X-ray diffraction and mass analyses, respectively. Financial support from *UGC*, New Delhi, to *N.P.* is gratefully acknowledged.

Experimental Part

General. TLC: silica gel *G* plates (SiO_2; *Merck*); petroleum ether (60–80°)/AcOEt as eluant. M.p.: in open capillary tubes; uncorrected. ^{1}H-, ^{13}C-, and 2D-NMR Spectra: *BrukerAvance* 300 MHz NMR instrument; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. Elemental analyses: *Perkin–Elmer-2400-II* CHNS elemental analyzer.

*Aryl(1*H*-indol-3-yl)methanones* **3** *and 1,3-Diaryl-1*H*-pyrazole-4-carboxaldehydes* **4**: *General Procedure.* Bis(aroylmethyl)sulfide bis(phenylhydrazone) **1** (1 mmol) is dissolved in DMF (5 ml), and the soln. is cooled to 0°. To the ice-cold soln., $POCl_3$ (2 mmol) is added dropwise, and the mixture is stirred for 30 min. The temp. is gradually increased to 80° and maintained for 2 h. After completion of the reaction (TLC), the mixture is cooled to r.t., and poured into ice-cold H_2O. The obtained solid is separated and purified by CC (SiO_2, petroleum ether (60–80°)/AcOEt 5:1): **3** and **4** (see *Table 1*).

*(1*H*-Indol-3-yl)phenylmethanone* (**3a**): Colorless solid. M.p. 242° ([6a]: 242–245°). ^{1}H-NMR: 7.23–7.31 (*m*, 2 arom. H); 7.55–7.64 (*m*, 4 arom. H); 7.81 (*d*, *J* = 7.2, 2 arom. H); 7.95 (*d*, *J* = 2.7, 1 arom. H); 8.28 (*dd*, *J* = 6.3, 1.8, 1 arom. H); 12.13 (*s*, NH). ^{13}C-NMR: 111.6; 114.5; 120.8; 121.2; 122.5; 125.7; 127.7 (2 C); 130.3; 135.0; 136.1; 140.0; 189.3.

*(1*H*-Indol-3-yl)(4-methylphenyl)methanone* (**3b**): Colorless solid. M.p. 180° ([7]: 179–180°). ^{1}H-NMR: 2.41 (*s*, Me); 7.24–7.28 (*m*, 2 arom. H); 7.35 (*d*, *J* = 8.1, 2 arom. H); 7.54 (*dd*, *J* = 6.6, 1.8, 1 arom. H); 7.72 (*d*, *J* = 8.1, 2 arom. H); 7.95 (*d*, *J* = 3.0, 1 arom. H); 8.26 (*dd*, *J* = 6.6, 1.8, 1 arom. H); 12.07 (*s*, NH). ^{13}C-NMR: 20.4; 111.5; 114.6; 120.8; 121.1; 122.4; 125.7; 127.9; 128.3; 134.6; 136.1; 137.3; 140.4; 189.1.

*(4-Chlorophenyl)(1*H*-indol-3-yl)methanone* (**3c**): Colorless solid. M.p. 240° ([6c]: 239–242°). ^{1}H-NMR: 7.19–7.27 (*m*, 2 arom. H); 7.51 (*dd*, *J* = 7.5, 2.1, 1 arom. H); 7.57 (*d*, *J* = 8.4, 2 arom. H); 7.79 (*d*, *J* = 8.4, 2 arom. H); 7.96 (br. *s*, 1 arom. H); 8.24 (*dd*, *J* = 7.5, 2.1, 1 arom. H); 12.12 (*s*, NH). ^{13}C-NMR: 111.8; 114.3; 120.9; 121.5; 122.7; 125.7; 128.0; 129.8; 135.3; 135.5; 136.2; 138.6; 188.2.

*(4-Bromophenyl)(1*H*-indol-3-yl)methanone* (**3d**): Colorless solid. M.p. 237°. ^{1}H-NMR: 7.21–7.29 (*m*, 2 arom. H); 7.52 (*dd*, *J* = 6.9, 1.8, 1 arom. H); 7.67–7.87 (*m*, 4 arom. H); 7.97 (*d*, *J* = 3.3, 1 arom. H); 8.24 (*d*, *J* = 6.9, 1.8, 1 arom. H); 12.18 (*s*, NH). ^{13}C-NMR: 111.6; 114.2; 120.8; 121.3; 122.6; 124.0; 125.5; 129.7; 130.7; 135.2; 136.1; 138.9; 188.1. Anal. Calc. for $C_{15}H_{10}BrNO$: C 60.02, H 3.36, N 4.67; found: C 59.98, H 3.33, N 4.64.

*(1*H*-Indol-3-yl)(4-methoxyphenyl)methanone* (**3e**): Colorless solid. M.p. 202° ([6b]: 203–205°). ^{1}H-NMR: 3.83 (*s*, MeO); 7.05 (*d*, *J* = 8.7, 2 arom. H); 7.19–7.25 (*m*, 2 arom. H); 7.49 (*dd*, *J* = 6.9, 1.8, 1 arom. H); 7.79 (*d*, *J* = 8.7, 2 arom. H); 7.93 (br. *s*, 1 arom. H); 8.20 (*dd*, *J* = 6.9, 1.8, 1 arom. H); 12.01 (*s*, NH). ^{13}C-NMR: 55.7; 112.5; 114.0; 115.4; 121.8; 122.0; 123.3; 126.8; 130.9; 133.3; 135.2; 136.9; 162.1; 188.2.

*([1,1′-Biphenyl]-4-yl)(1*H*-indol-3-yl)methanone* (**3f**): Colorless solid. M.p. 221°. ^{1}H-NMR: 7.22–7.26 (*m*, 2 arom. H); 7.40 (*t*, *J* = 7.2, 1 arom. H); 7.47–7.52 (*m*, 3 arom. H); 7.73 (*d*, *J* = 7.8, 2 arom. H); 7.80 (*d*, *J* = 8.4, 2 arom. H); 7.86 (*d*, *J* = 8.4, 2 arom. H); 8.00 (*d*, *J* = 3.0, 1 arom. H); 8.07 (*dd*, *J* = 6.6, 1.8, 1 arom. H); 12.09 (*s*, NH). ^{13}C-NMR: 111.6; 114.5; 120.8; 121.2; 122.5; 125.7; 125.9; 126.2; 127.4; 128.4; 128.5; 134.9; 136.1; 138.7; 138.8; 142.0; 188.8. Anal. calc. for $C_{21}H_{15}NO$: C 84.82, H 5.08, N 4.71; found: C 84.79, H 5.05, N 4.67.

*1,3-Diphenyl-1*H*-pyrazole-4-carboxaldehyde* (**4a**): Colorless solid. M.p. 138° ([4a]: 140°). ^{1}H-NMR: 7.36 (*t*, *J* = 7.2, 1 arom. H); 7.45–7.52 (*m*, 5 arom. H); 7.77 (*d*, *J* = 7.8, 2 arom. H); 7.82 (*dd*, *J* = 7.8, 1.5, 2 arom. H); 8.55 (*s*, 1 arom. H); 10.03 (*s*, CHO). ^{13}C-NMR: 119.6; 122.4; 127.8; 128.6; 128.9; 129.2; 129.5; 131.0; 131.3; 138.9; 154.6; 185.0.

*3-(4-Methylphenyl)-1-phenyl-1*H*-pyrazole-4-carboxaldehyde* (**4b**): Colorless solid. M.p. 121° ([4d]: 120–122°). ^{1}H-NMR: 2.42 (*s*, Me); 7.52 (*d*, *J* = 8.1, 2 arom. H); 7.38 (*t*, *J* = 7.5, 1 arom. H); 7.49 (*t*, *J* = 7.5, 2 arom. H); 7.71 (*d*, *J* = 8.1, 2 arom. H); 7.78 (*d*, *J* = 8.1, 2 arom. H); 8.52 (*s*, 1 arom. H); 10.04 (*s*, CHO). ^{13}C-NMR: 21.3; 119.7; 122.4; 127.8; 128.4; 128.8; 129.4; 129.6; 130.9; 139.0; 139.3; 154.8; 185.2.

*3-(4-Chlorophenyl)-1-phenyl-1*H*-pyrazole-4-carboxaldehyde* (**4c**): Colorless solid. M.p. 111° ([4d]: 110–113°). ^{1}H-NMR: 7.37–7.42 (*m*, 1 arom. H); 7.51 (*d*, *J* = 8.4, 2 arom. H); 7.64 (*d*, *J* = 8.4, 2 arom. H); 7.70–7.76 (*m*, 4 arom. H); 8.51 (*s*, 1 arom. H); 10.04 (*s*, CHO). ^{13}C-NMR: 119.5; 122.4; 123.9; 128.0; 129.6; 130.4; 130.9; 132.3; 132.8; 138.8; 153.2; 184.6.

*3-(4-Bromophenyl)-1-phenyl-1*H*-pyrazole-4-carboxaldehyde* (**4d**): Colorless solid. M.p. 140°. ^{1}H-NMR: 7.39 (*t*, *J* = 7.5, 1 arom. H); 7.52 (*t*, *J* = 7.5, 2 arom. H); 7.62 (*d*, *J* = 8.7, 2 arom. H); 7.74–7.79 (*m*, 4 arom. H); 8.53 (*s*, 1 arom. H); 10.03 (*s*, CHO). ^{13}C-NMR: 119.7; 122.5; 123.7; 128.1; 129.7; 130.3; 130.4; 131.8; 132.0; 138.9; 153.1; 184.3. Anal. calc. for $C_{16}H_{11}BrN_2O$: C 58.74, H 3.39, N 8.56; found C 58.71, H 3.36, N 8.52.

*3-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrazole-4-carboxaldehyde* (**4e**): Colorless solid. M.p. 102° ([4d]: 100–102°). ^{1}H-NMR: 3.86 (*s*, MeO); 7.02 (*d*, *J* = 8.7, 2 arom. H); 7.37 (*t*, *J* = 7.2, 1 arom. H); 7.49 (*t*, *J* = 7.2, 2 arom. H); 7.76–7.81 (*m*, 4 arom. H); 8.51 (*s*, 1 arom. H); 10.02 (*s*, CHO). ^{13}C-NMR: 55.3; 114.1; 119.6; 122.3; 123.8; 127.8; 129.6; 130.2; 131.2; 139.0; 154.4; 160.5; 185.1.

*3-([1,1′-Biphenyl]-4-yl)-1-phenyl-1*H*-pyrazole-4-carboxaldehyde* (**4f**): Colorless solid. M.p. 197°. ^{1}H-NMR: 7.36–7.42 (*m*, 2 arom. H); 7.45–7.54 (*m*, 4 arom. H); 7.66 (*d*, *J* = 7.5, 2 arom. H); 7.73 (*d*, *J* = 8.4, 2 arom. H); 7.81 (*d*, *J* = 7.5, 2 arom. H); 7.93 (*d*, *J* = 8.4, 2 arom. H); 8.56 (*s*, 1 arom. H); 10.10 (*s*, CHO).

^{13}C-NMR: 119.7; 122.6; 127.1; 127.4; 127.6; 128.0; 128.9; 129.3; 130.0; 130.2; 131.3; 139.0; 140.4; 142.1; 154.3; 185.0. Anal. calc. for $C_{22}H_{16}N_2O$: C 81.46, H 4.97, N 8.64; found: C 81.42, H 4.94, N 8.61.

Crystallographic Investigations[1]). Single crystals of **3c** for crystallographic studies were prepared in DMF. Crystallographic data for **3c** is given in *Table 2*.

Table 2. *Crystal Data of* **3c**

Empirical formula	$C_{15}H_{10}ClNO$	Absorption coefficient [mm^{-1}]	0.286
M_r	255.70	$F(000)$	528
Temperature [K]	295(2)	Crystal size [mm]	$0.20 \times 0.17 \times 0.13$
Wavelength [Å]	0.71073	θ Range for data collection [°]	2.79 to 26.56
Crystal system	monoclinic	Index ranges	$-17 \le h \le 17$, $-8 \le k \le 8$, $-13 \le l \le 17$
Space group	$P2_1/c$		
Unit-cell dimensions:		Reflections collected	13134
a [Å]	14.1025(6)	Independent reflections	2637 ($R_{int} = 0.0228$)
b [Å]	7.1469(3)	Completeness to $\theta = 60.00°$	99.8%
c [Å]	14.3196(6)	Max. and min. transmission	0.94 and 0.96
α [°]	90.000	Data, restraints, parameters	2637, 0, 163
β [°]	118.234(2)	Goodness-of-fit on F^2	1.018
γ [°]	90.000	Final R indices ($I > 2\sigma(I)$)	$R_1 = 0.0398$, $wR_2 = 0.1267$
Volume [Å^3]	1271.54(9)	R Indices (all data)	$R_1 = 0.0544$, $wR_2 = 0.1413$
Z	4	Largest diff. peak and hole	0.295 and -0.396
Density (calc.) [Mg/m^3]	1.336	[e Å^{-3}]	

REFERENCES

[1] W. Su, Y. Weng, L. Jiang, Y. Yang, L. Zhao, Z. Chen, Z. Li, J. Li, *Org. Prep. Proced. Int.* **2010**, *42*, 503.

[2] N. Paul, S. Muthusubramanian, *Tetrahedron Lett.* **2011**, *52*, 3743.

[3] V. Padmavathi, K. Mahesh, D. R. C. V. Subbaiah, A. Padmaja, *Heteroat. Chem.* **2008**, *19*, 261.

[4] a) M. A. Kira, M. O. Abdel-Rahman, K. Z. Gadalla, *Tetrahedron Lett.* **1969**, *10*, 109; b) A. M. Youssef, M. S. White, E. B. Villanueva, I. M. El-Ashmawy, A. Klegeris, *Bioorg. Med. Chem.* **2010**, *18*, 2019; c) B. F. Abdel-Wahab, R. E. Khidre, A. A. Farahat, *Arkivoc* **2011**, *i*, 196; d) O. Prakash, K. Pannu, A. Kumar, *Molecules* **2006**, *11*, 43; e) P. Rathelot, N. Azas, H. El-Kashef, F. Delmas, C. Di Giorgio, P. Timon-David, J. Maldonado, P. Vanelle, *Eur. J. Med. Chem.* **2002**, *37*, 671; f) O. Prakash, K. Pannu, R. Naithani, H. Kaur, *Synth. Commun.* **2006**, *36*, 3479; g) B. Insuasty, A. Tigreros, F. Orozco, J. Quiroga, R. Abonia, M. Nogueras, A. Sanchez, J. Cobo, *Bioorg. Med. Chem.* **2010**, *18*, 4965; h) R. Pundeer, P. Ranjan, K. Pannu, O. Prakash, *Synth. Commun.* **2009**, *39*, 316.

[5] N. Paul, M. J. Shanmugam, S. Muthusubramanian, *Synth. Commun.* **2013**, *43*, 129.

[6] a) D. M. Ketcha, G. W. Gribble, *J. Org. Chem.* **1985**, *50*, 5451; b) K. Sawada, S. Okada, A. Kuroda, S. Watanabe, Y. Sawada, H. Tanaka, *Chem. Pharm. Bull.* **2001**, *49*, 799; c) J. H. Wynne, C. T. Lloyd, S. D. Jensen, S. Boson, W. M. Stalick, *Synthesis* **2004**, 2277.

[7] A. R. Katritzky, K. Suzuki, S. K. Singh, H.-Y. He, *J. Org. Chem.* **2003**, *68*, 5720.

Received April 17, 2012

---

[1]) CCDC-824833 contains the supplementary crystallographic data (excluding structure factors) for **3c**. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/data_request/cif.