Indian Journal of Chemistry
Vol. 42B, July 2003, pp. 1738-1741

Note

Studies in Hantrsch thiazole synthesis: Synthesis of 3-(2-allylamino-4-thiazolyl)-2*H*-1-benzopyran-2-ones and 3-(4-phenylthiazoline-2-anil)-2*H*-1-benzopyran-2-ones in solid state

P Vijay Kumar, R Vinod Reddy & V Rajeswar Rao*

Department of Chemistry, National Institute of Technology (REC), Warangal 506 009, India.

Received 17 May 2002; accepted (revised) 20 August 2002

Interaction of 3-(2-bromoacetyl)coumarins with *N*-allylthiourea and diphenyl thiourea in solid state furnish corresponding 3-(2-allyl amino-4-thiazolyl)-2*H*-1-benzopyran-2-ones and 3-(4-phenyl thiazoline-2-anil)-2*H*-1-benzopyran-2-ones.

Many organic reactions are being rediscovered to occur in solid state processes like Baeyer-Villiger oxidation[1], $NaBH_4$ reduction of ketones[2], pinacol[3] and benzylic acid rearrangements[4] and wittig reaction[5] have recently been reported in solid state by Toda[6]. Yields are better than those in solution reaction and reactions are stereo selective too.

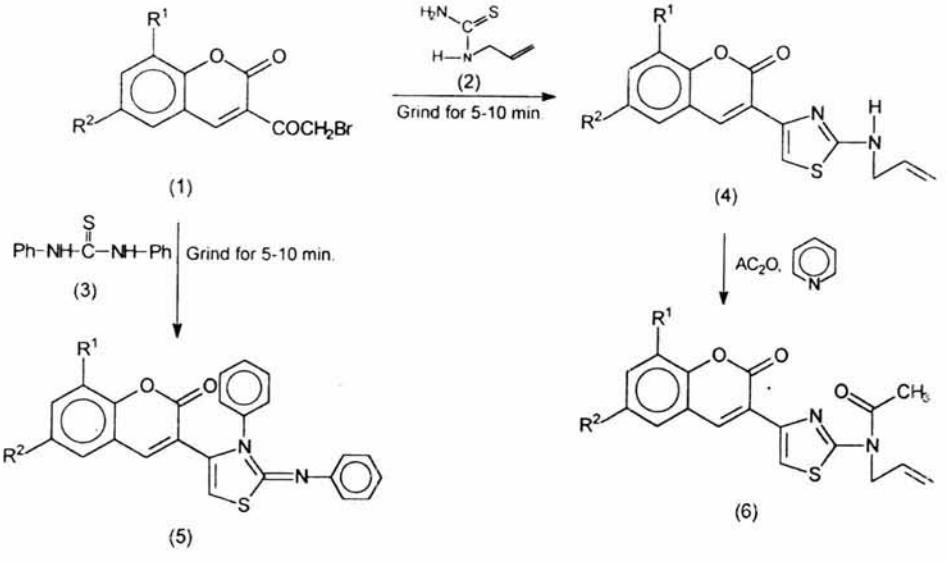
Thiazoles are generally synthesized by the Hantzsch thiazole synthesis from α-halogenoketones and thioureas or thioamides[7,8]. Later, King and co-workers[9,10] synthesized aminothiazoles by replacing α-halogenoketones with ketones and halogen. Despite this modification the method of King and co-workers is cumbersome and time-consuming (24-25 hr).

In view of these observations we report herein for the first time the Hantzsch thiazole synthesis in the absence of solvent in solid state at room temperature.

The Hantzsch condensation of 3-(2-bromoacetyl) coumarin[11] with *N*-allylthiourea and diphenylthiourea without any solvent at room temperature results in the rapid formation of the corresponding 3-(2-allyl amino-4-thiazolyl)-2*H*-1-benzopyran-2-ones and 3-(4-phenyl thiazoline-2-anil)-2*H*-1-benzopyran-2-ones in excellent yields (**Scheme I**). The reaction is fairly general, facile, efficient and is devoid of any side products.

In a typical case, a mixture of **1** and *N*-allylthiourea or diphenylthiourea was ground in a mortar by pestle at room temperature for about 10 min. The solid product obtained was combined with water and filtered off. After usual work-up title compounds were obtained in 80-90% yields.

When the condensation was carried out in anhydrous ethanol under reflux the yields are 60-70%. In all the cases the condensation proceeded much faster and more efficiently in the absence of solvent



Scheme I

than in solution. The reason is that in the absence of solvent has a high concentration of reagents so that the reaction goes faster. This is the simple procedure for the preparation of title compounds under very mild conditions with the advantage of (i) high yield (ii) manifold reduction in reaction time and (iii) solvent free conditions. The structures of 3-(2-allyl amino-4-thiazolyl)coumarins were further confirmed by converting them into their *N*-acetyl derivatives by treating them with acetic anhydride and few drops of pyridine. Finally all the compounds prepared were characterized on the basis of their analytical and spectral data.

In conclusion, the present method offers a convenient and potentially useful approach for the synthesis of thiazoles and thiazolines with appropriate substitution, which are important class of biodynamic agents. The method also provides better prospects in terms of yields, purity, short reaction period and simplicity of performance. The utility of this synthetic method is unlimited which can be extended to other thiazoles.

Experimental Section

All the melting points were uncorrected and recorded on cintex melting point apparatus. IR spectra were recorded in KBr on a Perkin-Elmer 337 spectrophotometer, ^{1}H-NMR spectra on a Varian Gemini 200 MHz spectrometer using TMS as internal standard (chemical shift values are expressed in δ, ppm) and mass spectra on a micromass instrument operating at 70 eV.

(a) General procedure for the preparation of 3-(2-allylamino-4-thiazolyl) and 3-(4-phenylthiazoline-2-anil)-2*H*-1-benzopyran-2-ones. 4, 5 in the absence of solvent. A mixture of 3-(2-bromoacetyl) coumarin **1** (0.01 mole), *N*-allylthiourea **2** or diphenylthiourea **3** (0.01 mole) was ground by pestle and mortar at room temperature for the period in **Table I**. The solid thus obtained was treated with water, filtered and recrystallized from appropriate solvent to give **4** and **5**.

4a: IR (KBr, ν_{max} in cm^{-1}): 1608 (-C=N-), 1720 (-O-C=O), and 3421(-NH-); ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 4.12 (d, 2H, $-CH_2$ –N-), 5.31 –5.51 (m, 2H, $=CH_2$), 5.85 –5.98 (1H, =CH), 7.30-7,37 (m, H_6 and H_8), 7.61-7.65 (m, 1H, H_7), 7.79-7.81 (2H, H_5 of coumarin and H_5' of thiazole), 8.89 (1H, C_4 of coumarin) and 9.53 (1H, -NH-, D_2O exchangeable); MS: (m/z) 284 (100%), 256 (44.5), 244 (11.2), 173 (20.5), 172 (64.3), 171 (15.6), 145 (5) and 101 (20).

4b: IR (KBr, ν_{max}, in cm^{-1}): 1610 (-C=N-), 1720 (lactone C=O) and 3420 (-NH-), ^{1}H NMR ($CDCl_3$): δ4.0 (s, 3H, OCH_3), 4.10 (d, 2H, CH_2-N-), 5.30-5.51 (m, 2H, $=CH_2$), 5.85 - 5.98 (1H, =CH), 7.10 - 7.30 (3H, Ar-H), 7.80 (1H, H_5' thiazole) 8.45 (s, 1H, C_4 of coumarin) and 9.50 (1H, -NH-, D_2O exchangeable).

5a: IR (KBr, ν_{max} in cm^{-1}): 1600 (-C=N-) and 1710 (lactone –C=O), ^{1}H NMR ($CDCl_3$): δ7.2 - 7.7 (m, 15H, Ar-H), 8.1 (s, 1H C_4 of coumarin).

5b: IR (KBr, ν_{max} in cm^{-1}): 1600 (-C=N-) and 1710 (lactone C=O), ^{1}H NMR ($CDCl_3$): δ4.0 (s, 3H,

Table 1—Hantzsch thiazole synthesis of **4** and **5** in the absence of solvent and in anhydrous ethanol

Compd	R^1 R^2	Reaction Period (min)	m.p. (°C)	Yield (%) without solvent	Yield (%) with solvent	Mol. formula (M.Wt.)	Found % (Calcd) N	Found % (Calcd) S
4a	H	10	120-125	90	70	$C_{15}H_{12}N_2O_2S$	9.82	11.21
	H					(284)	(9.86	11.26)
4b	OCH_3	8	162-165	88	66	$C_{16}H_{14}N_2O_3S$	8.84	10.00
	H					(314)	(8.41	10.19)
4c	H	8	227-230	85	68	$C_{15}H_{11}N_2O_2BrS$	7.68	8.78
	Br					(363)	(7.71	8.81)
4d	Br	6	198-200	87	65	$C_{15}H_{10}N_2O_2Br_2S$	6.30	7.20
	Br					(442)	(6.33	7.23)
4e	H	7	180-182	84	62	$C_{15}H_{11}N_2O_2ClS$	8.76	9.98
	Cl					(318.5)	(8.80	10.04)
4f	Cl	5	198-200	85	64	$C_{15}H_{10}N_2O_2Cl_2S$	7.90	9.00
	Cl					(353)	(7.93	9.06)
4g	5,6-benzo	5	218-220	80	60	$C_{19}H_{14}N_2O_2S$	8.35	9.54
						(334)	(8.38	9.58)

—Contd

Table I—Hantzsch thiazole synthesis of **4** and **5** in the absence of solvent and in anhydrous ethanol—*Contd*

Compd.	R^1 R^2	Reaction Period (min)	m.p. (°C)	Yield (%) without solvent	Yield (%) with solvent	Mol. formula (M.Wt.)	Found % (Calcd.) N	Found % (Calcd.) S
4h	OCH_3	7	318-320	82	62	$C_{16}H_{13}O_5N_3S$	11.66	8.87
	NO_2					(359)	(11.70	8.91)
4i	OCH_3	6	228-230	80	60	$C_{16}H_{13}O_3N_2SBr$	7.10	8.10
	Br					(393)	(7.12	8.14)
4j	(3′Nitro)	8	250-252	82	61	$C_{19}H_{13}O_4N_3S$	11.06	8.42
						(379)	(11.08	8.44)
5a	H	8	307-310	90	60	$C_{24}H_{16}O_2N_2S$	7.00	8.00
	H					(396)	(7.07	8.08)
5b	OCH_3	8	163-165	85	70	$C_{25}H_{18}O_3N_2S$	6.54	7.50
	H					(426)	(6.57	7.51)
5c	H	7	228-230	80	65	$C_{24}H_{15}O_2N_2SBr$	5.85	6.70
	Br					(475)	(5.89	6.73)
5d	Br	6	158-160	82	68	$C_{24}H_{14}O_2N_2SBr_2$	5.00	5.74
	Br					(554)	(5.05	5.77)
5e	H	8	153-155	84	64	$C_{24}H_{15}O_2N_2SCl$	6.46	7.40
	Cl					(430.5)	(6.50	7.43)
5f	Cl	5	190-192	88	68	$C_{24}H_{14}O_2N_2SCl_2$	6.00	6.84
	Cl					(465)	(6.02	6.88)
5g	5,6-benzo	6	318-320	90	70	$C_{28}H_{18}O_2N_2S$	6.20	7.10
						(446)	(6.27	7.17)
5h	OCH_3	8	138-140	85	65	$C_{25}H_{17}O_3N_2SBr$	5.50	6.30
	Br					(505)	(5.54	6.33)
5i	OCH_3	7	173-175	80	62	$C_{25}H_{17}O_5N_3S$	8.87	6.72
	NO_2					(471)	(8.91	6.79)
5j	3′-Nitro	6	310-320	82	61	$C_{28}H_{17}O_4N_3S$	8.31	8.48
	5,6-benzo					(491)	(8.55	6.51)
6a	H	—	173-175	—	88	$C_{17}H_{14}N_2O_3S$	8.54	9.79
	H					(326)	(8.58	9.81)
6b	OCH_3	—	158-160	—	82	$C_{18}H_{16}N_2O_4S$	7.82	8.94
	H					(356)	(7.86	8.98)
6c	H	—	158-160	—	85	$C_{17}H_{13}N_2O_3BrS$	6.87	7.88
	Br					(405)	(6.91	7.90)
6d	Br	—	168-170	—	84	$C_{17}H_{12}N_2O_3Br_2S$	5.74	6.60
	Br					(484)	(5.78	6.61)
6e	5,6-benzo	—	228-230	—	83	$C_{21}H_{16}N_2O_3S$	7.40	8.50
						(376)	(7.44	8.51)
6f	H	—	168-170	—	86	$C_{17}H_{13}N_2O_3ClS$	7.73	8.83
	Cl					(360.5)	(7.76	8.87)
6g	Cl	—	137-139	—	88	$C_{17}H_{12}N_2O_2Cl_2S$	7.00	8.09
	Cl					(395)	(7.08	8.10)
6h	OCH_3	—	174-175	—	83	$C_{18}H_{15}O_4N_2SBr$	6.40	7.31
	Br					(435)	(6.43	7.35)
6i	OCH_3	—	180-182	—	80	$C_{18}H_{15}O_6N_3S$	10.43	7.94
	NO_2					(401)	(10.47	7.98)

* All the compounds were recrystallized from methanol

OCH_3), 7.18 - 7.70 (m, 14H, Ar-H including 1H of thiazole) and 8.2 (s, 1H, C_4 of coumarin); MS: (m/z) 428 (m/z 20%), 427 (40%), 426 (100%), 425 (40%), 278 (31%), 263 (32%) and 235 (32%).

(b) General procedure for the preparation of *N*-acetyl derivatives of 4. *N*-acetyl derivatives of **4** were prepared by dissolving these compounds in the minimum amount of hot acetic anhydride and keeping the reaction mixture at room temperature for 24 hrs in the presence of catalytic amount of pyridine. The reaction mixture was then digested with cold water. The resulting solids were collected and purified by recrystallization from suitable solvents.

6a: IR (KBr, ν_{max} in cm^{-1}): 1604 (-C=N-), 1678 (CO-O-N), and 1717 (lactone –C=O), ^1H NMR ($CDCl_3$): δ2.4 (s, 3H, $NCOCH_3$), 4.95 (d, 2H, CH_2), 5.18 - 5.38 (m, 2H, $=CH_2$), 5.95 - 6.15 (m, 1H, =CH), 7.2 - 7.61 (m, 4H, Ar-H), 8.19 (s, 1H, C_5 of thiazole) and 8.44 (s, 1H, C_4 of coumarin).

6b: IR (KBr, ν_{max} in cm^{-1}): 1602 (C=N), 1684 (-CON-) and 1733 (lactone), ^1H NMR ($CDCl_3$): δ2.7 (s, 3H, $NCOCH_3$), 4.0 (s, 3H, OCH_3), 4.95 (d, 2H, $-CH_2$), 5.0 - 5.2 (m, 2H, $=CH_2$), 5.20 - 5.32 (m, 1H, =CH), 7.1 - 7.3 (m, 4H, including 1H of thiazole) and 8.4 (s, 1H, C_4 of coumarin).

6h: IR (KBr, ν_{max} in cm^{-1}): 1604 (-C=N-), 1678 (-CO-O-N-) and 1717 (lactone C=O), ^1H NMR ($CDCl_3$,): δ2.8 (s, 3H, $COCH_3$), 4.1 (s, 3H, OCH_3), 5.0 (d, 2H, $-CH_2-$), 5.2 - 5.3 (m, 2H, $=CH_2$), 5.3 - 5.35 (m, 1H, =CH), 7.15 - 7.35 (m, 3H, Ar-H, and 1H of thiazole) and 8.5 (s, 1H, C_4 of coumarin).

Acknowledgement

One of the authors (RVR) is grateful to UGC, New Delhi for the award of fellowship in the project.

References

1 Toda F, Yagi M & Kiyashige K, *J Chem Soc*, **1988**, 958.

2 Toda F, Kiyoshige K & Yagi M, *Angew Chem Intern Edu*, **1989**.

3 Toda F & Shigemasa T, *J Chem Soc Perkin Tran SI*, **1989**, 209.

4 Toda F, Tanaka K, Kagawa Y & Sakaino T, *Chem Lett*, **1990**, 373.

5 (a)Tomoskog I & Janzso G, *Chemy Ind*, (London), **1962**, 2085.

(b)Bestmann H & Lienrt, *J Chem Zig*, 94, **1970**, 487.

(c)Hanessian S, Delorme D, Beaudoin S & Leblance Y, *J Chem Soc*, 106, **1984**, 5754.

6 Toda F, *Syn Lett*, **1993**, 303.

7 Hantzsch A & Weber H J, *Ber dt Chem Ges*, 20, **1887**, 3118.

8 Hantzsch A, *Leibig's Ann*, 249, **1988**, 1.

9 Dadson R M & King L C, *J Am Chem Soc*, 67, **1945**, 2242.

10 King L C & Hlavacek R J, *J Am Chem Soc*, 72, **1950**, 3722.

11 Rajeswar Rao V & Padmanabha Rao T V, *Indian J Chem*, 25B, **1986**, 413.