Regioselective Syntheses of Functionalized 2-Aminopyridines and 2-Pyridinones through Nucleophile-Induced Ring Transformation Reactions[1]

Atul Goel,*[a] Fateh V. Singh,[a] Ashoke Sharon,[b] Prakas R. Maulik[b]

[a] Division of Medicinal and Process Chemistry, Central Drug Research Institute, Lucknow 226001, India
Fax +91(522)2623405; E-mail: agoel13@yahoo.com

[b] Division of Molecular and Structural Biology, Central Drug Research Institute, Lucknow 226001, India

Received 20 October 2004

Abstract: An efficient one-pot synthesis of 2-amino-6-aryl-4-methylsulfanylpyridines and 6-aryl-3-cyano-4-methylsulfanyl-2(1*H*)-pyridinone has been illustrated through ring transformation of 6-aryl-3-cyano-4-methylsulfanyl-2*H*-pyran-2-ones by urea through different reaction conditions. Various solvents and bases were employed to selectively prepare either 2-aminopyridines or 2-pyridinones. In case of direct fusion of 2*H*-pyran-2-one with urea in solvent-free conditions, both the products were obtained in 1:1 ratio, while the reaction in pyridine at reflux temperature exclusively afforded 2-aminopyridine in 80–90% yield. The reaction of 6-aryl-3-carbomethoxy-4-methylsulfanyl-2*H*-pyran-2-ones with urea at 150 °C afforded 2-pyridinone derivatives in good yield (70–80%).

Key words: 2-pyranone, 2-aminopyridine, 2-pyridinone, urea, ring transformation reaction

Pyridines and pyridinones are basic structural motifs found in numerous natural products having interesting medicinal properties.[2] Since molecules embedded with these scaffolds are known to exhibit molecular recognition[3] through non-covalent interactions, medicinal chemists exploited this information by simulating these bioactive units in the design of novel biologically active molecules. Diverse pharmacological activities[4–12] are associated with these heterocyclic compounds. In addition, 2-aminopyridines and 2-pyridinones are key intermediates in the synthesis of variety of heterocyclic compounds of therapeutic importance.[13]

Numerous synthetic methodologies for the synthesis of 2-aminopyridines have been reported, which include the condensation of α,β-unsaturated ketones with malononitrile in presence of ammonium acetate,[14] nucleophilic substitution of 2-halopyridines with primary or secondary amines,[15] aminolysis of 2-alkoxypyridines and [4+2] or [3+3] type ring formation reactions.[16] Recently, we have demonstrated efficient synthesis of 2-amino-3-cyanopyridines through base-catalyzed ring transformation of 2-pyranones with cyanamide.[17] Katritzky et al.[18] described the benzotriazole-assisted regioselective synthesis of 2-amino-3-unsubstituted-pyridines which were previously difficult to synthesize by conventional routes.

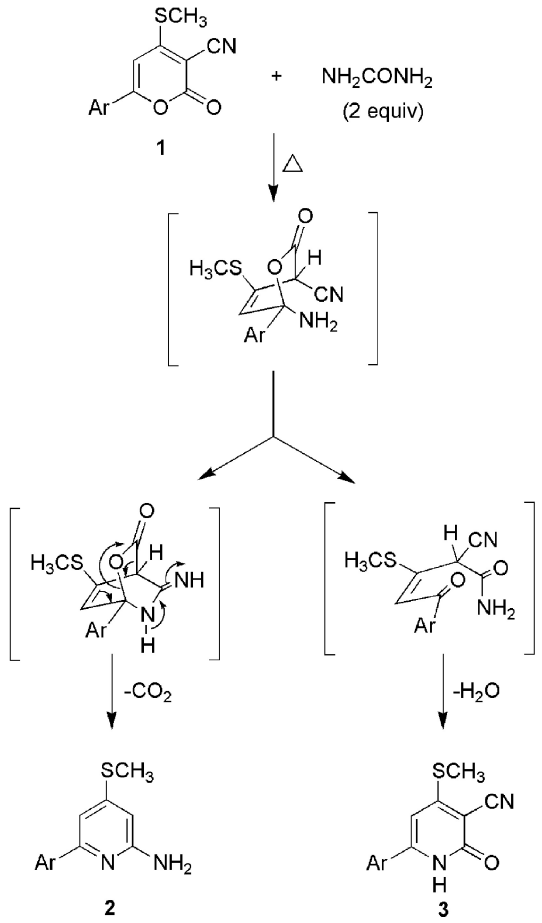
Literature procedures for the synthesis of 2-pyridinones include the oxidation of N-substituted pyridinium salts,[19] the reaction of β-dicarbonyl compounds or α,β-unsaturated ketones with malononitrile or similar active methylene compounds,[16,20] the reaction of α-oxoketenedithioacetals with cyanoacetamide in presence of a base,[21] the cycloaddition of 2-azadienes with acetylenic dienophiles,[22] the reaction of lithium dienediolates and nitriles,[23] and the reaction of acyl isocyanates and trimethylsilylketene.[24] Despite numerous synthetic methodologies available in the literature, none of them is sufficient in organic chemistry. Therefore, new, concise, economical, environmentally benign methods are always in demand.

Herein we report one-pot regioselective synthesis of 2-aminopyridines and 2-pyridinones through nucleophile-induced ring transformation of 2-pyranones by urea in good yield. As mentioned by Katritzky et al.,[18] 3-unsubstituted-2-aminopyridines are difficult to synthesize by commonly employed classical routes. Therefore, we have prepared 3-unsubstituted-2-aminopyridines selectively using urea as a source of nucleophile, which is economical and eco-friendly.

Due to their easy synthesis and high reactivity towards various nucleophiles in generating molecular diversity the chemistry of 2-pyranones has been recognized as a versatile approach which deviated from their classical synthetic procedures.[25] 2-Pyranones **1**, used as a parent precursor, have been conveniently prepared by the reaction of methyl 2-cyano-3,3-dimethylthioacrylate with acetophenone as described earlier.[26] The unique feature of lactone **1** is the presence of three electrophilic centers: C_2, C_4 and C_6 in which latter is highly susceptible to nucleophiles due to the extended conjugation and the presence of the electron-withdrawing substituent at position 3. The reactivity of **1** towards ambident nucleophiles has been explored by preparing substituted pyrazoles and isooxazoles using various amines.[26c,d] As urea is a good source of generating ammonia when heated to its melting point, we exploited the reaction of 2*H*-pyran-2-one with urea at elevated temperature in solvent-free condition.[27] Interestingly, two products, 2-aminopyridines **2** and 2-pyridinones **3**, were formed as shown in Scheme 1. The reaction proceeded very fast, which took few minutes for the formation of these heterocyclic compounds. Both compounds were isolated in 1:1 ratio by silica gel column chromatography using chloroform–hexane (1:1) as an eluent. The synthesis

SYNLETT 2005, No. 4, pp 0623–0626
Advanced online publication: 22.02.2005
DOI: 10.1055/s-2005-862365; Art ID: G38404ST

of functionalized 2-aminopyridines and 2-pyridinones in one-pot using economical reagents may have importance in lead identification process by generating libraries in a short time.



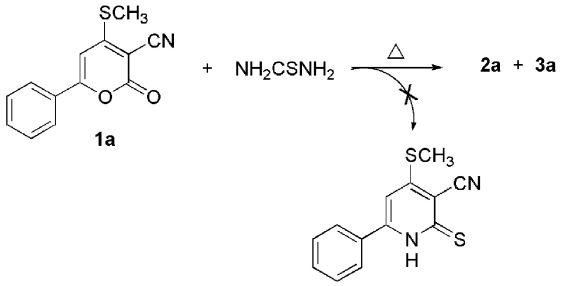
Scheme 1

Table 1 Yields of 2-Aminopyridines (**2**) and 2-Pyridinones (**3**)

Entry	Ar	Reaction time (min)	Yield (%)[a]	
			2	**3**
a	C_6H_5	15	38	43
b	4-FC_6H_4	8	41	46
c	4-ClC_6H_4	10	40	47
d	4-BrC_6H_4	12	39	45
e	4-$CH_3C_6H_4$	12	41	43
f	4-$OCH_3C_6H_4$	13	44	43
g	Furyl	11	39	46
h	Thienyl	15	41	45

[a] All the reactions were carried out at 150 °C under solvent-free conditions.

The plausible reaction mechanisms for the formations of 2-aminopyridines and 2-pyridinones are depicted in Scheme 1. The reaction is possibly initiated by attack of the ammonia, generated in situ from urea to the highly vulnerable electrophilic center C_6 of 2-pyranone. At this juncture, the reaction may proceed in two different ways. The synthesis of 2-aminopyridine implied that the amino group present on the diene intermediate attacked at the nitrile functionality to form a cyclic intermediate, followed by aromatization and decarboxylation to yield 2-amino-6-aryl-4-methylsulfanylpyridine (**2**) in moderate yield (Table 1). Similarly, the reaction to form 2-pyridinone proceeded through intramolecular cyclization involving the amino and carbonyl functionalities of the 2-pyranone intermediate followed by dehydration to afford 6-aryl-3-cyano-4-methylsulfanyl-2(1*H*)-pyridinone (**3**) in moderate yield.



Scheme 2

There may be another mechanism for the formation of 2-pyridinone **3**. Urea may directly attack at C_6 position of 2-pyranone, followed by ring opening, decarboxylation and recyclization involving the carbonyl group of urea and the C_3 position of 2-pyranone and subsequent elimination of ammonia to yield 2-pyridinone. In order to prove that the carbonyl group of 2-pyridinone came from 2-pyranone and not from urea, an independent reaction of 2-pyranone **1a** and thiourea was carried out as shown in Scheme 2. Interestingly, we isolated the same products (**2a** and **3a**) as obtained by the reaction with urea. No 2-thiopyridinone compound was isolated from the reaction mixture. This reaction clearly indicated that the carbonyl group of 2-pyridinone was derived from 2-pyranone as described in Scheme 1. The structure of 2-pyridinone, obtained by the reaction with thiourea was unambiguously confirmed by X-ray crystallography.[28]

The conformation of the compound **3a**, as determined by X-ray crystallography, demonstrated various non-covalent interactions, in which NH and CO functionalities form a dimer by strong intermolecular H-bonds (Figure 1). The crystal-packing diagram of **3a** revealed the presence of offset parallel aromatic π-π stacking as shown by centroid separation. Thus, the combination of strong H-bonding and aromatic interaction stabilizes the molecule in the crystalline state. These types of interactions play a significant role in crystal engineering and supramolecular chemistry.

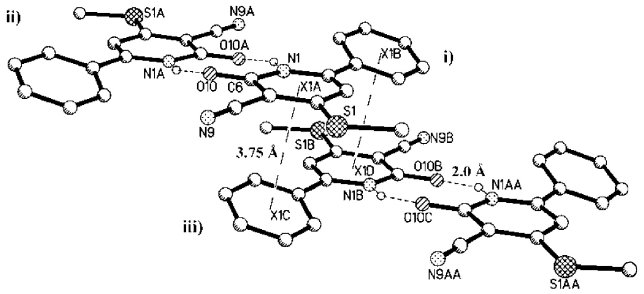
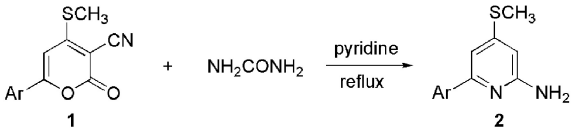


Figure 1 The part of crystal packing diagram of **3a** showing dimerization (**i** and **ii**) by intermolecular strong H-bonding between NH and CO functionality (N-H…O = 2.0 Å, < NHO = 160.4) in a same plane and further title molecule interacted by means of offset parallel intermolecular aromatic stacking (**i** and **iii**) shown by centroid separation (X1A…X1C or vice versa X1B…X1D = 3.75 Å) [symmetry code for **i**): x, y, z; **ii**) 1-x, 2-y, 1-z; **iii**) –x, 2-y, 1-z].

The lack of regioselectivity under solvent-free reaction conditions prompted us to examine the course of reaction in different solvents using various inorganic bases. Several polar or non-polar solvents such as ethanol, DMF, DMSO, fluorobenzene, pyridine, toluene were employed in combination with various bases such as KOH, K_2CO_3, NaH, *t*-BuOK and NaOEt, majority of them leads to mixture of compounds with different side products. Interestingly, the reaction of **1** with urea in pyridine at reflux temperature afforded selectively 2-aminopyridine derivatives in high yield as shown in Scheme 3 and Table 2. The preference for the formation of 2-aminopyridines over 2-pyridinones is possibly due to the solvation effect and basic nature of the pyridine.



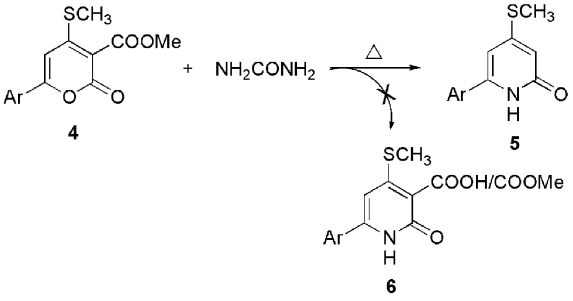
Scheme 3

Table 2 Reaction of 2-Pyranones **1** with Urea

2	Ar	Reaction time (h)	Mp (°C)	Yield (%)[a]
a	C_6H_5	15	136–138	91
b	4-FC_6H_4	24	142–144	87
c	4-ClC_6H_4	24	118–119	90
d	4-BrC_6H_4	21	126–127	92
e	4-$CH_3C_6H_4$	19	98–99	88
f	4-$OCH_3C_6H_4$	21	80–82	87
g	Furyl	19	134–136	89
h	Thienyl	25	Oil	82

[a] All the reactions were carried out in pyridine at reflux temperature without using a base.

To the best of our efforts, we could not selectively prepare 2-pyridinones **3** using 2-pyranone **1** and urea. Through the reaction mechanism described in Scheme 1, we found that the nitrile functionality present on 2-pyranone **1** is playing a leading role in the preparation of 2-aminopyridine **2**. We thought that the replacement of the nitrile group with a methoxycarbonyl functionality should analogously yield 2-pyridinone exclusively.



Scheme 4

Table 3 Reaction of 6-Aryl-3-carbomethoxy-4-methylsulfanyl-2*H*-pyran-2-one (**4**) with Urea

5	Ar	Reaction time (min)	Mp (°C)	Yield (%)[a]
a	C_6H_5	13	133–134	70
b	4-FC_6H_4	10	182–183	72
c	4-$CH_3C_6H_4$	15	133–134	78
d	2-Thienyl	10	220–221	80
e	2-Pyridyl	12	160–162	76

[a] All the reactions were carried out at 150 °C under solvent-free conditions.

To explore this possibility the reaction of 6-aryl-3-carbomethoxy-4-methylsulfanyl-2*H*-pyran-2-one (**4**) with urea at 150 °C in solvent-free condition was carried out (Scheme 4). It was interesting to note that under the same reaction conditions as described in Scheme 1, the reaction afforded only 6-aryl-4-methylsulfanyl-1*H*-pyridin-2-one (**5**) in good yield (Table 3). No product with 3-carboxylic or carbomethoxy-pyridinone **6** was formed. The plausible mechanism for the formation of pyridinone **5** may be similar to the mechanism proposed for the formation of 2-aminopyridine **2** shown in Scheme 1. All the synthesized derivatives were characterized by elemental and spectroscopic analyses.[28]

In conclusion, our procedure for the preparation of 2-aminopyridines and 2-pyridinones from the reaction of 2-pyranones and urea is very simple and economical. We have regioselectively prepared 2-aminopyridines through nucleophile-induced ring transformation of 6-aryl-3-cyano-4-methylsulfanyl-2*H*-pyran-2-ones by urea using pyridine as a reaction solvent. The 2-pyridinone derivatives were obtained in good yields by direct fusion of 6-aryl-3-carbomethoxy-4-methylsulfanyl-2*H*-pyran-2-ones and urea.

Acknowledgement

Authors thank Department of Science and Technology (DST), New Delhi, for financial support and members of Sophisticated Analytical Instrumentation Facility (SAIF), CDRI, Lucknow, for providing elemental analyses and spectroscopic data of synthesized compounds.

References

(1) C.D.R.I. Communication No. 6544.
(2) (a) Smith, D. In *Comprehensive Organic Chemsitry*, Vol. 4; Sames, P. G., Ed.; Pergamon: Oxford, **1979**, 3. (b) Bailey, T.; Goe, G.; Scriven, E. In *Heterocyclic Compounds*, Part 5, Vol. 14; Newkome, G. R., Ed.; Wiley: New York, **1984**, 215. (c) Fodor, G. B.; Colasanti, B. In *Alkaloids: Chemical and Biological Perspectives*, Vol. 3; Pelletier, S. W., Ed.; Wiley: New York, **1985**, 1–90.
(3) (a) Spivak, D. A.; Shea, K. J. *Anal. Chim. Acta* **1999**, *435*, 4627. (b) Kròl, I.; Rospenk, M.; Sobczyk, L. *J. Mol. Struct.* **2000**, *552*, 312. (c) Sugeta, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3706.
(4) Niño, A.; Muñoz-Caro, C.; Carbò-Dorca, R.; Gironés, X. *Biophys. Chem.* **2003**, *104*, 417.
(5) Sata, N.; Shibata, T.; Jitsuoka, M.; Ohno, T.; Takahashi, T.; Hirohashi, T.; Kanno, T.; Iwaasa, H.; Kanatani, A.; Fukami, T. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1761.
(6) Carlsson, C.; Rosen, I.; Nilsson, E. *Acta Anaesthesiol. Scand.* **1993**, *27*, 87.
(7) (a) Curran, D.; Liu, H. *J. Am. Chem. Soc.* **1992**, *114*, 5863. (b) Schultz, A. *Chem. Rev.* **1973**, *73*, 385. (c) Kelly, T.; Bell, S.; Osashi, N.; Armstrong-Chong, J. *J. Am. Chem. Soc.* **1988**, *110*, 6471.
(8) (a) Cox, R.; O'Hagan, D. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2537. (b) Rigby, J.; Balasubramanian, N. *J. Org. Chem.* **1989**, *54*, 224.
(9) Williams, D.; Lowder, P.; Gu, Y.-G. *Tetrahedron Lett.* **1997**, *38*, 327.
(10) Teshima, Y.; Shin-ya, K.; Shimazu, A.; Furihota, K.; Chul, H. S.; Furihata, K.; Hayakawa, Y.; Nagai, K.; Seto, H. *J. Antibiot.* **1991**, *44*, 685.
(11) Matyus, P.; Kasztreiner, E.; Diesler, E.; Behr, A.; Varga, I.; Kosary, J.; Rabloczky, G.; Jaszlits, L. *Arch. Pharm.* **1994**, *327*, 543.
(12) Narusevicius, E.; Garaliene, V.; Krauze, A.; Duburs, G. *Khim. Farm. Zh.* **1989**, *23*, 1459.
(13) (a) Tieckelmann, H. In *Heterocyclic Compounds, Pyridine and its Derivatives*, Supplement Part 3; Abramovitch, R. A., Ed.; Wiley-Intersciences: New York, **1974**, 597. (b) Murray, T.; Zimmerman, S. *Tetrahedron Lett.* **1995**, *36*, 7627.
(14) (a) Sakurai, A.; Midorikawa, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 430. (b) Latif, N.; Girgis, N. S. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1981**, *20*, 147.
(15) (a) Vorbrüggen, H. *Adv. Heterocycl. Chem.* **1990**, *49*, 117. (b) Matsumoto, K.; Minatogawa, H.; Munakata, M.; Toda, M.; Tsukube, H. *Tetrahedron Lett.* **1990**, *27*, 3923. (c) Matsumoto, K.; Hashimoto, S.; Otani, S. *J. Chem. Soc., Chem. Commun.* **1991**, 306.
(16) (a) McKillop, A.; Boulton, A. J. In *Comprehensive Heterocyclic Chemistry*, Vol. 2; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon Press: New York, **1984**, 67. (b) McKillop, A.; Boulton, A. J. In *Comprehensive Heterocyclic Chemistry*, Vol. 2; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon Press: New York, **1984**, 460–463.
(17) Farhanullah Agarwal, N.; Goel, A.; Ram, V. J. *J. Org. Chem.* **2003**, *68*, 2983.
(18) Katritzky, A. R.; Belyakov, S. A.; Sorochinsky, A. E.; Henderson, S. A.; Chen, J. *J. Org. Chem.* **1997**, *62*, 6210.
(19) (a) Decker, H. *Chem. Ber.* **1892**, *25*, 443. (b) Mohrle, H.; Weber, H. *Tetrahedron* **1970**, *26*, 2953.
(20) Jones, G. In *Comprehensive Heterocyclic Chemistry*, Vol. 2; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon Press: New York, **1984**, 395.
(21) Rastogi, R. R.; Kumar, A.; Ila, H.; Junjappa, H. *J. Chem. Soc., Perkin Trans. 1* **1978**, 549.
(22) Ghosez, L.; Jnoff, E.; Bayard, P.; Sainte, F.; Beaudegnies, R. *Tetrahedron* **1999**, *55*, 3387.
(23) Brun, E. M.; Gil, S.; Mestres, R.; Parra, M. *Synthesis* **2000**, 273.
(24) Takaoka, K.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1996**, *37*, 4973.
(25) (a) Ram, V. J.; Goel, A. *Chem. Lett.* **1997**, *10*, 1021. (b) Nath, M.; Srivastava, P.; Goel, A.; Ram, V. J. *Eur. J. Org. Chem.* **1998**, 2083. (c) Srivastava, P.; Saxena, A. S.; Ram, V. J. *Synthesis* **2000**, 544. (d) Ram, V. J.; Srivastava, P. *Curr. Org. Chem.* **2001**, *5*, 571.
(26) (a) Tominaga, Y.; Ushirogouchi, A.; Matsuda, Y.; Kobayashi, G. *Chem. Pharm. Bull.* **1984**, *32*, 3384. (b) Tominaga, Y.; Ushirogouchi, A.; Matsuda, Y. *J. Heterocycl. Chem.* **1987**, *24*, 1557. (c) Ram, V. J.; Verma, M.; Hussaini, F. A.; Shoeb, A. *J. Chem. Res., Synop.* **1991**, 98. (d) Ram, V. J.; Hussaini, F. A.; Singh, S. K.; Shoeb, A. *J. Chem. Res., Synop.* **1993**, 110.
(27) **Synthesis of 2-Amino-6-aryl-4-methylsulfanyl-pyridines (2a–h) and 6-Aryl-3-cyano-4-methylsulfanyl-2 (1*H*)-pyridinones (3a–h), General Procedure.**
A mixture of 6-aryl-3-cyano-4-methylsulfanyl-2*H*-pyran-2-ones (**1**, 1 mmol) and urea (2.3 mmol) was fused at 150 °C for 5–15 min. After completion, the reaction was cooled to r.t. and H_2O was added (10 mL) to give the crude compound. The pure compounds were isolated on silica gel column, using $CHCl_3$–hexane (1:1) as eluent.
(28) **Spectroscopic and Elemental Analyses Data of Selected Compounds.**
Compound **2a**: yellow solid; mp 136–138 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.50 (s, 3 H, SCH_3), 4.23 (br s, 2 H, NH_2), 6.30 (s, 1 H, PyH), 6.90 (s, 1 H, PyH), 7.41–7.44 (m, 3 H, ArH), 7.87–7.90 (m, 2 H, ArH). IR (KBr): 3430 cm^{-1} (NH_2). MS (FAB): 217 [M^+ + 1]. Anal. Calcd for $C_{12}H_{12}N_2S$: C, 66.63; H, 5.59; N, 12.95. Found: C, 66.69; H, 5.61; N, 12.83.
Compound **3a**: CCDC No. 238556; white solid; mp >250 °C. ^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.73 (s, 3 H, SCH_3), 6.61 (s, 1 H, CH), 7.56–7.59 (m, 3 H, ArH), 7.83–7.87 (m, 2 H, ArH), 12.50 (br s, 1 H, NH). IR (KBr): 1645 (CO), 2214 (CN), 3444 cm^{-1} (NH). MS (FAB): 243 [M^+ + 1]. Anal. Calcd for $C_{13}H_{10}N_2OS$: C, 64.44; H, 4.16; N, 11.56. Found: C, 64.66; H, 4.28; N, 11.62.
Compound **5c**: white solid; mp 133-134 °C. ^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.44 (s, 3 H, CH_3), 2.56 (s, 3 H, SCH_3), 6.12 (s, 1 H, CH), 6.47 (s, 1 H, CH), 7.31 (d, *J* = 8.0 Hz, 2 H, ArH), 7.62 (d, *J* = 8.0 Hz, 2 H, ArH), 11.50 (br s, 1 H, NH). IR (KBr): 1628 (CO), 3383 cm^{-1} (NH). MS (FAB): 232 [M^+ + 1]. Anal. Calcd for $C_{13}H_{13}NOS$: C, 67.50; H, 5.66; N, 6.06. Found: C, 67.62; H, 5.69; N, 6.18.