

MICROWAVE ENHANCED SYNTHESIS OF 5-ARYLIDENE RHODANINE UNDER SOLVENT FREE CONDITIONS USING BISMUTH TRICHLORIDE AS A PROMOTER

Ravinder S. Bhatti^a, Manjit Singh^a and Jagir S. Sandhu^{b*}

^aDepartment of Pharmaceutical Sciences and Drug Research,
Punjabi University, Patiala-147 002, India

^bDepartment of Chemistry, Punjabi University, Patiala-147 002, India
Email: j_sandhu2002@yahoo.com

ABSTRACT

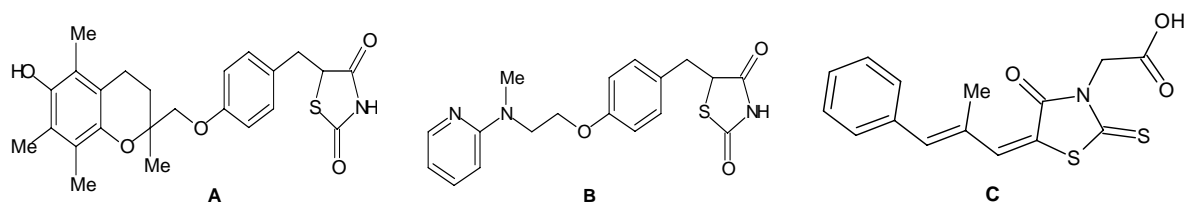
Aldehydes are condensed with rhodanine under solvent free condition using BiCl_3 yielding 5-arylidene rhodanines in excellent yields. Green approach involved here is solvent free and microwave enhancement.

Keyword: BiCl_3 , rhodanines, 2,4-thiazolidinedione, solvent free, microwave, aldehydes

INTRODUCTION

Use of Multicomponent reactions (MCRs) is the need of present century and is primarily driven by pharmaceutical industrial¹ needs. Also present-day concern is the development of green processes because of pollution avoiding awareness and fast developments are there to develop solvent free processes². These methodologies are being adopted for reducing time, money, energy and these are eco-friendly. The Multicomponent reactions are being explored vigorously during last two decades or so.

Search for insulin sensitizing agents is of immense interest for many years³. As a result of these efforts few new generation antidiabetic agents⁴ like Troglitazone (**A**), Rosiglitazone (**B**), Epalrestat (**C**) are now commercially available as antidiabetic agents (Scheme 1).



Scheme-1

From the structural features of **A**, **B** and **C** it is well clear that all these clinically used antidiabetic drugs do contain crucial segment of the molecules which is obtained via Knoevenagel condensation of rhodanines (2,4-thiazolidinedione) with various aldehydes. Apart from antidiabetic activity, rhodanine derivatives possess outstanding pharmacological activities^{5,6} such as antiviral, antimicrobial, and anticonvulsant effect. Additionally, rhodanine based molecules serves as Hepatitis C virus (HCV) protease inhibitor⁷, Uridine diphospho-*N*-acetylmuramate/L-alanine ligase⁸ inhibitor. Because of this commercial importance, the Knoevenagel condensation of rhodanine with aldehydes have been a subject of considerable interest and to effect this condensation efficiently, large number of catalysts have been explored⁹⁻¹¹ sodium acetate in glacial acetic acid, piperidinium benzoate in refluxing toluene, morpholine with acetic acid, zeolite, tetrabutyl ammonium bromide (TBAB), refluxing reactants in toluene at 110 °C for 3 days. Certainly these processes can't be taken as facile and efficient for the synthesis of 5-arylidene rhodanines as they require long reaction times, high temperature and products are obtained in unsatisfactory yields. In continuation to our interest in mild eco-friendly Lewis acids, we and others have been developing BiCl_3 as mild Lewis acid in organic synthesis^{12a}. This has emerged as promising eco-

friendly, non-toxic Lewis acid catalyst including Knoevenagel reactions^{12b}. In this communication, we are disclosing the use of this catalyst in rhodanine condensation with aldehydes.

EXPERIMENTAL

Melting points were recorded in open capillaries and are uncorrected. IR spectra were recorded in KBr discs on a Perkin-Elmer 240C analyzer. ¹H NMR spectra were recorded on Varian Gemini 300 (300 MHz) spectrometer in DMSO-d₆ using TMS as internal standard. The progress of reaction was monitored by TLC using silica gel G (Merck). Aldehydes were procured from commercial source and used without further purification. Rhodanine and 2,4-thiazolidinedione were purchased from Fluka. 3-methyl-5-phenylpyrrazol-5-one was prepared according to literature procedure.

General procedure under solvent free condition:

Aldehyde (2 m mol) and active methylene compound (2 m mol) and BiCl₃ (10 mol%) were placed in small conical flask and mixed with glass rod at room temperature. The mixture was then exposed to microwave radiations at 800 W for time given in Table 1. After completion of reaction (monitored via TLC), the reaction mixture was cooled to room temperature. Added 15 ml of water, stirred for 5 minute. The solid thus obtained was filtered, dried and recrystallized from ethanol to afford product.

Selected spectral data:

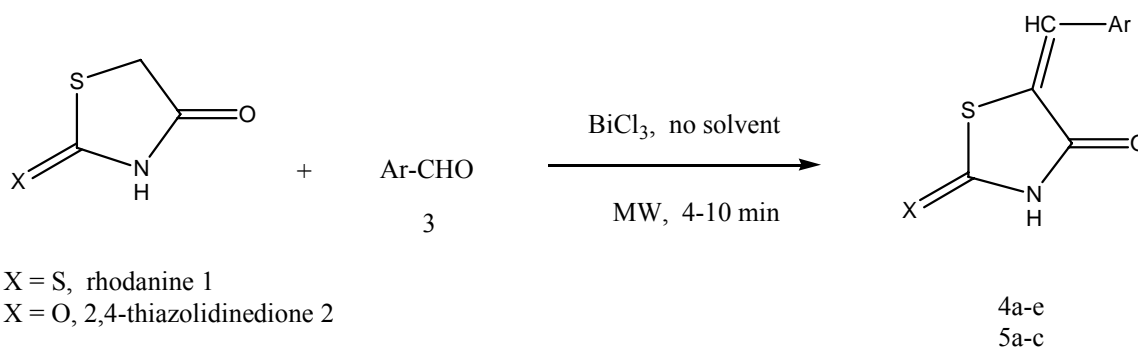
5-Benzylidene rhodanine (**4a**): mp. 204-206 °C: ¹H NMR (300 MHz, DMSO-d₆) δ_H: 13.57 (s, 1H, NH), 7.68 (s, 1H, =CH), 7.48-7.79 (m, 5H, Ar-H); IR (KBr): 3390, 1709, 1669, 1600, 1429, 1200 cm⁻¹.

5-(4-Methoxybenzylidene) rhodanine (**4d**): 244-246 °C: ¹H NMR (300 MHz, DMSO-d₆) δ_H: 13.71 (s, 1H, NH), 7.61 (s, 1H, =CH), 7.52 (d, 2H, *j* = 8.2 Hz, Ar-H), 7.08 (d, 2H, *j* = 8.2 Hz, Ar-H), 3.09 (s, 3H, OCH₃).

5-(4-Methylbenzylidene) -2,4-thiazolidinedione (**5b**): 215-217 °C: ¹H NMR (300 MHz, DMSO-d₆) δ_H: 12.50 (s, 1H, br, NH), 7.69 (s, 1H, =CH), 7.50 (d, 2H, *j* = 8.3 Hz, Ar-H), 7.11 (d, 2H, *j* = 8.3 Hz, Ar-H), 3.49 (s, 3H, OCH₃); IR (KBr) 3211, 1725, 1689 cm⁻¹.

RESULT AND DISCUSSION

Because of the commercial importance of clinically used drugs **A**, **B** and **C** which employ Knoevenagel reaction at the condensation step involving aldehyde and rhodanine, we were prompted to use BiCl₃ as a mild Lewis acid in this step. Indeed we succeeded and condensation products were obtained in excellent yield.

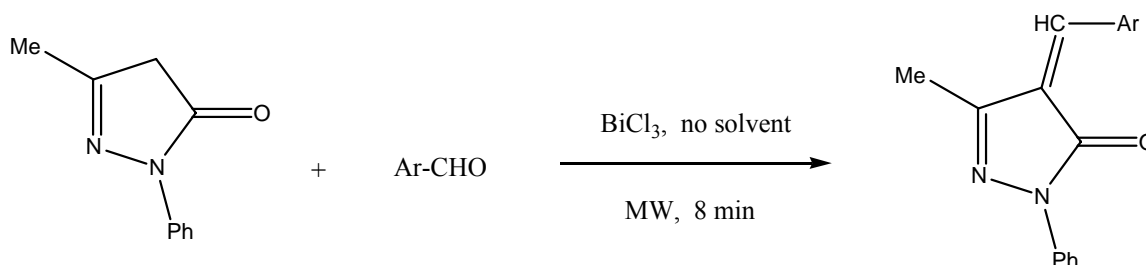


Scheme-2

In a typical experimental procedure, rhodanine (2 mmol) and benzaldehyde (2 mmol) and BiCl₃ (0.2 m mol) were placed in small conical flask and mixed with glass rod at room temperature. The mixture was then exposed to microwave radiations at 800 W for 5 minutes. After completion of reaction (monitored via TLC), the reaction mixture was cooled to room temperature. Added 15 ml of water, stirred for 5 minute. The solid thus obtained was filtered, dried and recrystallized from ethanol to afford 5-benzylidene rhodanine **4a** in 88 % yield, mp 204-206 °C Lit mp 204- 206 °C. Similarly other aromatic aldehydes were

condensed with rhodanine following similar procedure to obtained 5-arylidene rhodanines **4b-e** in 84-90 % yields. This protocol is fairly large in scope, yields are very good and use of microwave has shortened the reaction from hours to minutes.

Encouraged by these results we extended this protocol to other 5-membered heterocycles like 2,4-thiazolidinedione **2** and 3-methyl-1-phenylpyrazol-5-one **6**. The condensation of 2,4-thiazolidinedione with aldehydes completes within 7-8 minutes and the 5-arylidene thiazolidinediones **5a-c** were obtained in 85-92 % yield (Table 1, entry 6-8). When 3-methyl-1-phenylpyrazol-5-one was condensed with anisaldehyde,



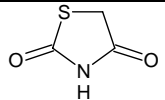

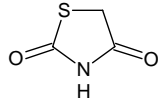
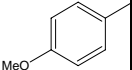
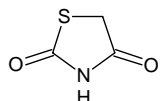
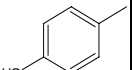
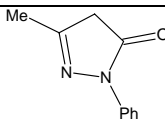
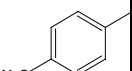
4-anisylidene-3-methyl-1-phenylpyrazol-5-one was obtained in 85 % yield and reaction completes in 9 minute (Scheme 3, Table 1, entry 9). All the compounds thus obtained are well characterized with physical and spectral techniques and the data compares well with corresponding compounds obtained through known techniques.

CONCLUSION

In conclusion, we have developed a quick, clean and simple method for the synthesis of 5-arylidene rhodanines, 5-arylidene thiazolidinediones and 4-arylidene pyrazol-5-ones. It employs mild Lewis acid BiCl_3 catalyst, it is fairly general, yields are also very high, time involved is few minutes, Overall this new procedure is fairly attractive as it is economical as well as a green process.

Table-1: BiCl_3 catalyzed condensation of active methylene compounds with aldehydes using microwave irradiation under solvent free conditions

Entry	Substrate	Ar	Products ^a	Time (min)	Yield ^b (%)	M.Pt (°C) ^c
1			4a	5	90	204-206 (204-206) ¹³
2			4b	4	85	229-231 (231-232) ¹³
3			4c	4	90	263-265 (263-264) ¹¹
4			4d	8	88	244-246 (240-246) ¹¹
5			4e	7	89	217-219 (219-220) ¹³

6			5a	7	92	246-248 (247-249) ¹⁴
7			5b	8	84	215-217 (218) ¹⁴
8			5c	8	87	294-297 (>300) ¹⁴
9			7	10	85	126-128 (127-128) ¹⁴

^aAll products were characterized by m.p. and spectral techniques and finally with mixed m.p. with authentic samples; ^bIsolated yield; ^cValues in parenthesis are lit. M.Pt.

REFERENCES

- (a) R A Sheldon, *Chem. Ind (London)* 12(1997).(b) J H Clark, *Chemistry of waste minimization, (Chapman and Hall, London)*, 1995(c) J H Clark, & D J Macquarrie, *Chem Soc Rev* 303(1996)
- (a) F Toda, K Tanaka & A Sekikawa. *J Chem. Soc. Chem Commun*, 279(1987).(b) For reviews on solvent free organic synthesis see: (1) F Todda, *Acc Chem Res* 480(1995). (2) K Tanaka & F Todda, *Chem Rev*, 1024(2000).(c) D C Dittmer, *Chem Ind* 779(1997).(d) N Hall, *Science* **266**, 32(1994)
- T. Sohda, K. Mizumo, E. Imamiya, H. Tawada, K. Meguro, Yamamoto Y. Kawamastu, *Chem. Pharm. Bull* **30**, 3601(1982)
- M. J. Reginato and M. A. Lazar, *TEM*, **10**, 9(1999); B. B. Zhang and D. E. Muller, *Current Opinion in Chemical Biology*, **4**, 461(2000)
- S. K. Shukla, S. P. Singh, L. P. Awasthi and D. D. Mukherjee, *Indian J. Pharm. Sci.*, **44**, 153(1982);*Chem. Abstr.* **99**, 22365u (1983)
- G. Capan, N. Ulusoy, N. Ergenc, A. C. Ekinic and A. Vidin, *Il Farmaco*, **51**, 729(1996);*Chem. Abstr.*, **126**, 157436q (1996)
- W. T. Sing, C. L. Lee, S. L. Yeo, S. P. Lim and M. M. Sim, *Biorg. Med. Chem. Lett.* **11**, 91(2001)
- M. M. Sim, S. B. Ng, A. D. Buss, S. C. Crasta, K. L. Goh and S. K. Lee, *Biorg. Med. Chem. Lett*, **12**, 697(2002); G Bruna, L. Costantino, C. Curinga, R. Maccari, F. Monforte, F. Nicolo, R. Ottana and M. G. Vigorita, *Bioorg. Med. Chem. Lett.*, **12**, 1077(2002)
- D. Libermann, J. Himbert and L. Hengl, *Bull. Soc. Chim. France*, **4**, 1120(1948); D. A. Heerding, L. T. Christmann, T. J. Clark, D. J. Holmes, S. F. Rittenhouse, D. T. Takata and J. W. Venslavsky, *Bioorg. Med. Chem. Lett*, **13**, 3771(2003); K. Popov-Pergal, Zh. Chekovich and M. Pergal, *Zhur. Obshch. Khim* **61**, 2112(1994)
- A. Corma, V. Forne, R. M. Martin-Aranda, H. Garcia and Primo, *J. Appl. Catal.* **59**, 237(1990); J. Muzart, *Synth. Commun* **15**, 285(1985)
- J.-F. Zhou, F.-X. Zhu, Y.-Z. Song and Y.-L. Zhu, *ARKIVOC* (xiv), 175(2006)
- (a) D. Prajapati and J.S. Sandhu, *Chemistry Letters* 1945(1992); B. Baruah, D. Prajapati, A Baruah and J.S. Sandhu, *Tetrahedron Letters* 1449-1450(1997).(b) M. Wada, H. Ohki, K. Y. Akiba, *Bull. Chem. Soc. Jpn.* **63**, 1738(1990); H. Suzuki, T. Ikegami, Y. Matano, *Synthesis* 249(1997), S. Vidal, *Synlett Spotlight* 31, *Synlett* 1194(2001).
- M. Sortino, P. Delgado, S. Juarez, J. Quiroga, R. Abonia, B. Insuasty, M. Nogueras, L. Rodero, F. M. Garibotto, R. D. Enriz and S. A. Zacchino, *Bioorg. Med. Chem.* **15**, 484(2007).

- 14 R. G. Giles, N. J. Lewis, J. K. Quick, M. J. Sasse, M. W. J. Urquhart and L. Youssef, *Tetrahedron*, **56**, 4531(2000); G. W. Sawdey, M. K. Ruoff and P. W. Vittum, *J. Am. Chem. Soc.*, **72**, 4947(1950).

(Received: 29 September 2008

Accepted: 11 October 2008

RJC-254)

RASĀYAN

Journal of Chemistry

...has been abstracted (right from its first issue) in the following abstracting agencies-

- AQUATIC SCIENCE AND FISHERIES ABSTRACTS (USA)
- CAB ABSTRACTS (UK)
- CHEMICAL ABSTRACTS (USA)
- CSA ILLUMINA NATURAL SCIENCES (USA)
- GLOBAL HEALTH (UK)
- INDIAN SCIENCE ABSTRACTS (INDIA)
- MEDICINAL AND AROMATIC PLANT ABSTRACTS (INDIA)
- NANOTECHNOLOGY ABSTRACTS (USA)
- POLLUTION ABSTRACTS (USA)
- RUSSIAN PERIODICALS CATALOG
- ULRICH'S PERIODICALS DIRECTORY (USA)
- WATER RESOURCES ABSTRACTS (USA)

Thanks to all Editors, Referees, Contributors, Readers and Critics for being with us and to motivate us to achieve this success. Thank you very much for your encouraging co-operation. Please feel free to write your opinion or feedback to- rasayanjournal@gmail.com.