A FACILE ONE STEP SYNTHESIS OF 3-(3-METHYL-ISOXAZOLO[4,5-*B*] PYRIDIN-*N*-OXIDE-6-YL)CHROMEN-2-ONES AND THEIR DEOXYGENATION

E. Rajanarendar*, D. Karunakar, P. Ramesh & E. Kalyan Rao
Department of Chemistry, Kakatiya University, Warangal – 506 009, India.

Abstract : A simple and efficient method has been developed for the synthesis of chromene substituted isoxazolo[4,5-*b*]pyridine-*N*-oxides **3** from 3,5-dimethyl-4-nitroisoxazole **1** and substituted 3-acetyl-2-oxo-2*H*-3-chromenes **2** in presence of piperidine. Pyridin-*N*-oxides **3** are deoxygenated to corresponding pyridines **4** by treatment with PCl_3.

Introduction

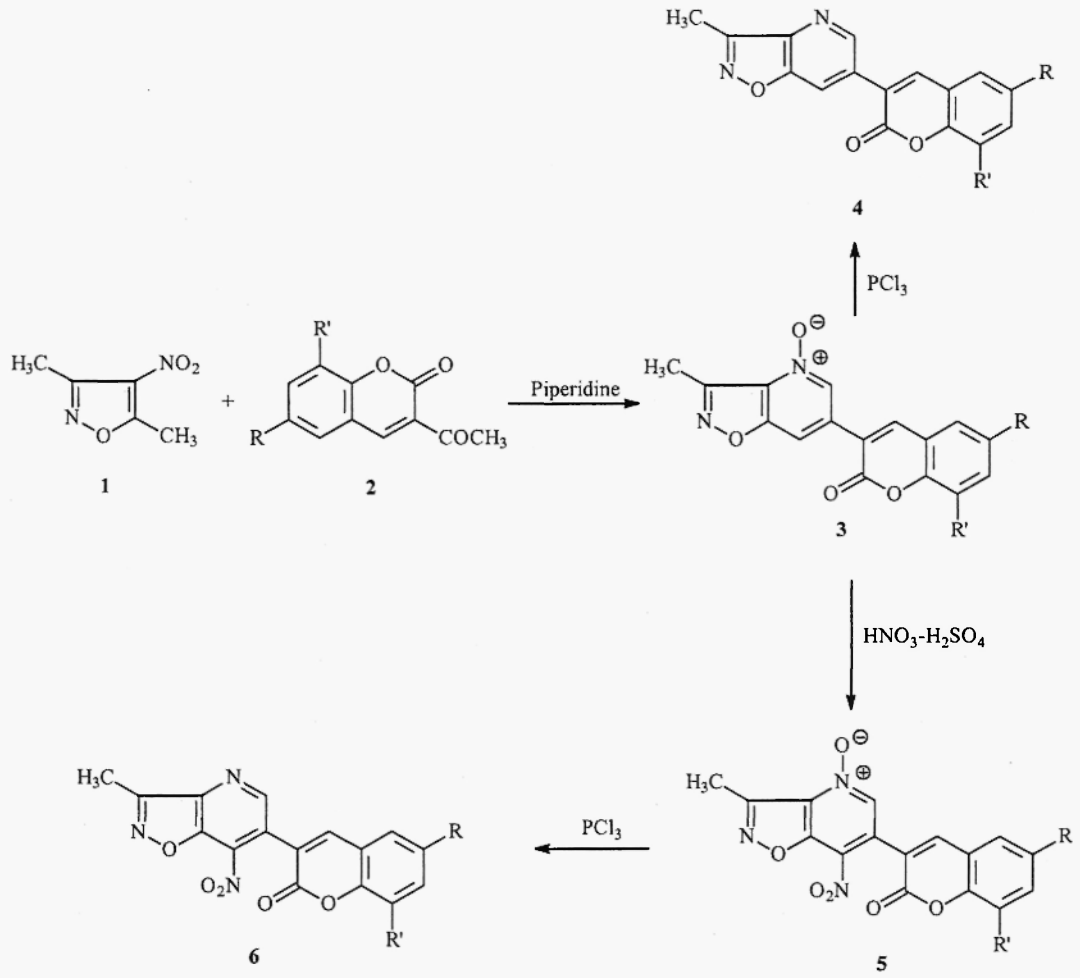
Different ring closure approaches for the preparation of the isoxazolo[4,5-*b*]pyridine system have been studied from suitably substituted 4-aminoisoxazoles[1,2], ortho-difunctionalized pyridine derivatives[3,4] and 3,5-dimethyl-4-nitroisoxazole[5,6]. We have reported the synthesis of isoxazolo[4,5-b]pyridine-N-oxides by condensation-cyclisation processes of 3,5-dimethyl-4-nitro-isoxazole with the β-dicarbonyl compounds in one step reaction[7,8]. Pyridine-*N*-oxides on deoxygenation gives corresponding pyridines. This happens to be the easiest and shortest route for the synthesis of isoxazolo[4,5-b]pyridines. As a sequel to our work on development of new methodologies for the synthesis of different substituted isoxazolo-[4,5-*b*]pyridines, we herein report the synthesis of new chromene substituted isoxazolo[4,5-*b*]pyridines by a shortest route.

Results and Discussions

3,5-Dimethyl-4-nitroisoxazole **1** undergoing a regioselective styrylation of the 5-methyl group only, when treated with aromatic aldehydes in the presence of piperidine, is a well investigated reaction[9-12]. The reaction of 3,5-dimethyl-4-nitro isoxazole **1** with 3-acetyl-2-oxo-2*H*-3-chromene **2** in presence of piperidine afforded 3-(3-methyl-isoxazolo[4,5-*b*]pyridin-*N*-oxide-6-yl)-chromen-2-one **3** in a single step. Different substituted chromene derivatives have been utilized in this reaction to get title compounds. This provides ample evidence for the generality of the reaction to make different chromene substituted isoxazolo[4,5-*b*]pyridine-*N*-oxides. The reaction is fairly general, facile and efficient and is devoid of any side products. The deoxygenation of pyridine-*N*-oxides **3** has been carried out by heating with PCl_3, which resulted in corresponding pyridines **4**. In general, the deoxygenated products had lower melting points than the *N*-oxides. This is due to disappearance of highly polar *N*-oxide moiety in the reduced products.

Nitration of **3** produced 7-nitroderivative **5**, a characteristic reaction of *N*-oxides, which reverse the polarity in pyridine and activates the 2- and 4-positions towards electrophilic substitution reactions. Later, **5** also deoxygenated to corresponding pyridine **6** easily by treatment with PCl_3.

^{1}H NMR spectrum of the product **3a** showed three singlets δ 2.2, 7.2 and 8.1 due to methyl and C-7 and C-5 protons of *N*-oxide ring. Chromene ring proton appeared as a singlet at δ 8.4. IR spectrum showed the *N*-oxide peak at 1420 cm^{-1}. The mass spectrum showed the molecular ion peak at m/z 294 indicating the formation of pyridine-*N*-oxide.



3 & 4 a, R = R' = H
3 & 4 b, R = H, R' = OCH_3
3 & 4 c, R = Cl, R' = H
3 & 4 d, R = Br, R' = H
3 & 4 e, R = R' = Cl
3 & 4 f, R = R' = Br
5, R = R' = H
6, R = R' = H

Scheme-1

Formation of alkyl anion from initially formed styryl compound, by base promoted deprotonation of active methylene hydrogen followed by nucleophilic attack of the latter on the nitro group and finally the dehydration resulted in the formation of product **3**.

^{1}H NMR spectrum of the pyridine **4a** showed three singlets at δ 2.3, 7.6 and 8.5 due to methyl and C-7 and C-5 protons of pyridine ring. The downfield shift in the signals of pyridine ring hydrogens of C-7 and C-5 in comparison to its counterpart *viz.*, pyridine-*N*-oxide reflects the electron withdrawing nature of pyridine ring. Chromene ring proton appeared as a singlet at δ 8.1. IR spectrum did not show the absorption due to *N*-oxide moiety instead it showed C=N stretching at 1640 cm^{-1}. The mass spectrum agrees with the pyridine structure by showing molecular ion peak at m/z 278.

In ^{1}H NMR spectrum of **5**, the vinylic hydrogen of pyridine ring (C-7) was absent confirming nitration. The mass spectrum of **5** confirmed nitration by showing the molecular ion peak at m/z 339. The deoxygenated product **6**, also did not show any resonance around δ 7.2 in its ^{1}H NMR spectrum confirming nitration at postion-7. Compound **6** showed the molecular ion at m/z 323 in its mass spectrum.

In conclusion, we have demonstrated an elegant one step synthesis of fused isoxazolo[4,5-*b*]pyridine-*N*-oxides by using easily available nitroisoxazole **1**, which is an excellent synthon for building of this binuclear system, which are later deoxygenated to corresponding pyridines easily by treatment with PCl_3. Moreover, this happens to be the first report on the synthesis of isoxazolo[4,5-*b*]pyridines substituted with a heterocyclic system.

Experimental

Melting points determined on a Cintex melting point apparatus and are uncorrected. The purity of the compounds was checked by TLC. IR spectra was recorded in KBr (cm^{-1}) on a Perkin Elmer spectrum BX series FT-IR spectrometer, ^{1}H NMR spectra on a Varian Gemini 300 MHz spectrometer using tetramethyl silane as internal standard in $CDCl_3$ on δ scale and mass spectra on a Jeol JMC D-300 spectrometer. C, H and N analyses were carrid out on a Carlo Erba 106 and Perkin-Elmer model 240 analysers.

Preparation of 3-(3-methyl-isoxazolo[4,5-b]-pyridin-N-oxide-6-yl)-chromen-2-ones 3a-f:
3,5-Dimethyl-4-nitroisoxazole **1** (0.01 mole) and 3-acetyl coumarine **2** (0.01 mole) were refluxed in methanol (10 mL) containing piperidine (1 mL) for 8 hr. The solvent was distilled off and the gummy material obtained was triturated with light petrol repeatedly then it is treated with ice-cold methanol to give solid product. Recrystallization from methanol.

Preparation of 3-(3-methyl-isoxazolo[4,5-*b*]-pyridin-6-yl)-chromen-2-ones 4a-f:
A solution of PCl_3 (1 mL) in chloroform (5 mL) was added dropwise to isoxazolo[4,5-b]pyridine-N-oxide (0.01 mole) in chloroform (5 mL). The mixture was refluxed for 4 hr. under anhydrous conditions. The solution was poured in ice water, made basic with NaOH. It was extracted with chloroform. Removal of solvent gave the solid, which was recrystallized from benzene-ethylacetate.

Preparation of 3-(3-methyl-7-nitro-isoxazole[4,5-*b*]-pyridin-*N*-oxide-6-yl)-chromen-2-one 5 :
Compound **4** (0.01 mole) was dissolved in conc. H_2SO_4 (2.5 mL). To this mixture with slow stirring, fuming HNO_3 (0.5 mL) was added dropwise by keeping the contents in ice-bath to maintain the temperature at 10°C. The mixture was heated to 95°C for 2 hr. on oil-bath. This was cooled and poured into ice-water with stirring. The separated light yellow compound was treated with aq. Na_2CO_3 solution. Recrystallization from methanol afforded light yellow crystals of **5**.

Preparation of 3-(3-methyl-7-nitro-isoxazolo[4,5-*b*]pyridin-6-yl)-chromen-2-one 6 :
A solution of PCl_3 (1.0 mL) in chloroform (6 mL) was added dropwise to compound **5** (0.01 mole) in chloroform (6 mL). The mixture was stirred at room temperature for 3 hr and refluxed for 1 hr under anhydrous conditions. The solution was cooled and poured in ice-water, and made basic with NaOH. It was then extracted with chloroform. Removel of the solvent gave the solid, which was recrystallized from methanol to give **6**.

Physical and analytical data for compound **3, 5** and **6** are presented in **Table-1**.

Table 1 : Physical and analytical data of 3-(3-methyl-isoxazolo[4,5-*b*]-pyridin-*N*-oxide-6-yl)-chromen-2-ones **3,** 3-(3-methyl-isoxazolo[4,5-*b*]pyridin-6-yl)-chromen-2-ones **4, 5** and **6**.

Compd	R	R'	Yield (%)	m.p. (°C)	Mol. formula	Found (%) Calcd. C	H	N
3a	H	H	60	220	$C_{16}H_{10}N_2O_4$	65.24 (65.30	3.36 3.40	9.54 9.52)
3b	H	OCH_3	62	232	$C_{17}H_{12}N_2O_5$	62.99 (62.96	3.73 3.70	8.66 8.64)
3c	Cl	H	55	241	$C_{16}H_9N_2O_4Cl$	58.41 (58.44	2.70 2.73	8.54 8.52)
3d	Br	H	58	253	$C_{16}H_9N_2O_4Br$	51.43 (51.47	2.38 2.41	7.48 7.50)
r3e	Cl	Cl	60	267	$C_{16}H_8N_2O_4Cl_2$	52.92 (52.89	2.17 2.20	7.68 7.71)
3f	Br	Br	56	276	$C_{16}H_8N_2O_4Br_2$	42.49 (42.47	1.73 1.76	6.21 6.19)
4a	H	H	58	132	$C_{16}H_{10}N_2O_3$	69.02 (69.06	3.61 3.59	10.08 10.07)
4b	H	OCH_3	60	141	$C_{17}H_{12}N_2O_4$	66.20 (66.23	3.91 3.89	9.12 9.09)
4c	Cl	H	54	150	$C_{16}H_9N_2O_3Cl$	61.40 (61.44	2.85 2.88	8.94 8.96)
4d	Br	H	55	158	$C_{16}H_9N_2O_3Br$	53.70 (53.78	2.50 2.52	7.82 7.84)
4e	Cl	Cl	56	164	$C_{16}H_8N_2O_3Cl_2$	55.30 (55.33	2.31 2.30	8.08 8.06)
4f	Br	Br	54	171	$C_{16}H_8N_2O_3Br_2$	44.06 (44.03	1.85 1.83	6.40 6.42)
5	H	H	60	258	$C_{16}H_{19}N_3O_6$	56.59 (56.63	2.63 2.65	12.36 12.38)
6	H	H	55	154	$C_{16}H_9N_3O_5$	59.40 (59.44	2.76 2.78	12.96 13.00)

Spectra of representative compounds

3a : IR (KBr) : 1420 ($=N^+-O^-$), 1722 (lactone C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) : δ 2.21 (s, 3H, CH_3), 7.23 (s, 1H, C-7 H), 8.12 (s, 1H, C-5 H), 8.40 (s, 1H, chromene-H), 7.32-8.45 (m, 4H, Ar-H), EIMS : m/z M^+ 294.

3b : IR (KBr) : 1426 ($=N^+-O^-$), 1726 (lactone C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) : δ 2.12 (s, 3H, CH_3), 4.02 (s, 3H, OCH_3), 7.35 (s, 1H, C-7 H), 8.1 (s, 1H, C-5 H), 8.6 (s, 1H, chromene-H), 7.4-8.3(m, 3H, Ar-H), EIMS : m/z M^+ 308.

3c : IR (KBr) : 1431 ($=N^+-O^-$), 1732 (lactone C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) : δ 2.24 (s, 3H, CH_3), 7.35 (s, 1H, C-7 H), 8.22 (s, 1H, C-5 H), 8.61 (s, 1H, chromene-H), 7.45-8.23 (m, 3H, Ar-H), EIMS : m/z M^+ 328.

3d : IR (KBr) : 1428 ($=N^+-O^-$), 1729 (lactone C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) : δ 2.25 (s, 3H, CH_3), 7.20 (s, 1H, C-7 H), 8.11 (s, 1H, C-5 H), 8.56 (s, 1H, chromene-H), 7.55-8.20 (m, 3H, Ar-H), EIMS : m/z M^+ 372.

3e : IR (KBr) : 1439 ($=N^+-O^-$), 1738 (lactone C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) : δ 2.15 (s, 3H, CH_3), 7.30 (s, 1H, C-7 H), 8.25 (s, 1H, C-5 H), 8.56 (s, 1H, chromene-H), 7.75 (s, 1H, Ar-H), 8.14 (s, 1H, Ar-H). EIMS : m/z M^+ 362.

3f : IR (KBr) : 1433 ($=N^+-O^-$), 1735 (lactone C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) : δ 2.35 (s, 3H, CH_3), 7.21 (s, 1H, C-7 H), 8.24 (s, 1H, C-5 H), 8.65 (s, 1H, chromene-H), 7.82 (s, 1H, Ar-H), 8.00 (s, 1H, Ar-H). EIMS : m/z M^+ 450.

4a : IR (KBr) : 1640 (C=N), 1718 (lactone C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) : δ 2.32 (s, 3H, CH_3), 7.65 (s, 1H, C-7 H), 8.50 (s, 1H, C-5 H), 8.63 (s, 1H, chromene-H), 7.35-8.04 (m, 4H, Ar-H). EIMS : m/z M^+ 278.

4b : IR (KBr) : 1646 (C=N), 1724 (lactone C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) : δ 2.40 (s, 3H, CH_3), 3.92 (s, 3H, OCH_3), 7.55 (s, 1H, C-7 H), 8.50 (s, 1H, C-5 H), 8.72 (s, 1H, chromene-H), 7.45-8.12 (m, 3H, Ar-H). EIMS : m/z M^+ 308.

4c : IR (KBr) : 1651 (C=N), 1728 (lactone C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) : δ 2.33 (s, 3H, CH_3), 7.60 (s, 1H, C-7 H), 8.50 (s, 1H, C-5 H), 8.65 (s, 1H, chromene-H), 7.61-8.02 (m, 3H, Ar-H). EIMS : m/z M^+ 312.

4d : IR (KBr) : 1642 (C=N), 1726 (lactone C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) : δ 2.40 (s, 3H, CH_3), 7.51 (s, 1H, C-7 H), 8.62 (s, 1H, C-5 H), 8.80 (s, 1H, chromene-H), 7.45-8.15 (m, 3H, Ar-H). EIMS : m/z M^+ 356.

4e : IR (KBr) : 1656 (C=N), 1733 (lactone C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) : δ 2.30 (s, 3H, CH_3), 7.52 (s, 1H, C-7 H), 8.50 (s, 1H, C-5 H), 8.65 (s, 1H, chromene-H), 7.52 (s, 1H, Ar-H), 8.02 (s, 1H, Ar-H). EIMS : m/z M^+ 346.

4f : IR (KBr) : 1648 (C=N), 1731 (lactone C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) : δ 2.40 (s, 3H, CH_3), 7.62 (s, 1H, C-7 H), 8.62 (s, 1H, C-5 H), 8.70 (s, 1H, chromene-H), 7.65 (s, 1H, Ar-H), 7.91 (s, 1H, Ar-H). EIMS : m/z M^+ 434.

5 : IR (KBr) : 1400 ($=N^+-O^-$), 1720 (lactone C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) : δ 2.40 (s, 3H, CH_3), 8.40 (s, 1H, C_5-H), 8.80 (s, 1H, chromene-H), 7.30-7.85 (m, 4H, Ar-H), EIMS : m/z M^+ 339.

6 : IR (KBr) : 1720 (lactone C=O) cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) : δ2.35 (s, 3H, CH_3), 8.42 (s, 1H, C_5-H), 8.78 (s, 1H, chromen-H), 7.25-8.00 (m, 4H, Ar-H), EIMS : m/z 323 M^+.

Acknowledgements

The authors thank Director, IICT, Hyderabad for the ^1H NMR and mass spectral data and CIC, Kakatiya University, Warangal for the IR spectra. One of the authors (DK) acknowledge the financial support of the CSIR, New Delhi.

References

1. K. Gewald, P. Bellmann, H.J. Jansch, *Leibigs Ann. Chem.* 1623 (1980).
2. A. Camparini, F. Ponticelli, P. Tedeschi, *J. Chem. Soc. Perkin Trans.*, **1**, 2391 (1982).
3. Y. Tagawa, Y. Goto, *Heterocycles,* **26**, 2921 (1987).
4. J. Drummond, G. Johnson, D.G. Nickell, D.F. Ortwine, R.F. Bruns, B. Welbaum, *J. Med. Chem.*, **32**, 2116 (1989).
5. R. Nesi, D. Giomi, S. Turchi, P. Tedeschi, *Synth Commun.* **22(16)**, 2349 (1992).
6. T.J.M. Chary, A.K. Murthy, E. Rajanarendar, *Indian J. Chem.* **42B**, 1742 (2003).
7. E. Rajanarendar, M. Srinivas, K. Ramu, *Synth. Commun.* **33(17)**, 3077 (2003).
8. E. Rajanarendar, M. Srinivas, P. Ramesh, K. Ramu, *Indian J. Chem.*, **44B**, 1927 (2005).
9. A.K. Murthy, K.S.R.K.M. Rao, N.V.S. Rao, *Indian J. Chem.*, **11**, 1074 (1973).
10. A.K. Murthy, K.S.R.K.M. Rao, N.V.S. Rao, *Indian. J. Appl. Chem.*, **35**, 90 (1972).
11. P. Umadevi, N.V.S. Rao, *Indian Acad. Sci.*, **84(2)**, 79 (1976).
12. K. Kashima, H. Yamamoto, R. Tsuda, *Heterocycles*, **6**, 805 (1977).

Received on January 30, 2006