Molecules **2007**, *12*, 797-804

molecules

ISSN 1420-3049
http://www.mdpi.org

Full Paper

Synthesis of α,β-Unsaturated Ketones as Chalcone Analogues *via* a $S_{RN}1$ Mechanism

Christophe Curti, Armand Gellis and Patrice Vanelle*

Laboratoire de Chimie Organique Pharmaceutique, UMR CNRS 6517, Université de la Méditerranée, Faculté de Pharmacie, 27, boulevard Jean Moulin, 13385 Marseille Cedex 05, France

* Author to whom correspondence should be addressed;
E-mail: patrice.vanelle@pharmacie.univ-mrs.fr

Received: 13 February 2007; in revised form: 14 April 2007 / Accepted: 16 April 2007 / Published: 18 April 2007

Abstract: An electron-transfer chain reaction between 2-nitropropane anion and α-bromoketones derived from nitrobenzene and nitrothiophene was demonstrated by mechanistic study and a specific convenient synthetic protocol. Thus, 2-bromo-1-(5-nitrothiophen-2-yl)ethanone or 2-bromo-1-(4-nitrophenyl)ethanone were reacted with several cyclic nitronate anions to form α,β-unsaturated ketones *via* a $S_{RN}1$ mechanism. This new method can be used to synthesize a wide variety of chalcone analogues.

Keywords: $S_{RN}1$, nitrothiophene, nitrophenylethanone, α,β-unsaturated ketones, chalcones.

Introduction

α,β-Unsaturated ketones are useful key intermediates [1,2] bearing the well-known chalcone pharmacophore. Chalcones can be isolated from several plants, and are precursors of flavones and anthocyan compounds. Some of them exhibit antioxidant and anticancer properties. In fact, the pharmacological properties of chalcones are due to the presence of both α,β-unsaturation [3] and an aromatic ring. It was noticed that among the recently published chalcones possessing antimicrobial activity, several are *para*-nitrosubstituted derivatives [4-7].

Using a retrosynthetic approach, the synthesis of such structures from α-bromocarbonyl compounds was developed with the $S_{RN}1$ methodology . Usually, such an electron-tranfer chain reaction between 2-nitropropane anion and halomethyl substrates led to a mixture of a *C*-alkylation product and an ethylenic compound resulting from nitrous acid elimination from the former alkylation product [8-10].

Since Russell and Ros's electron transfer reaction studies [11], it seemed possible to apply $S_{RN}1$ methodology to α-halocarbonyl compounds. Accordingly, we have established a convenient synthesis of α,β-unsaturated ketones **5** and **6** by the reaction of α-bromoketones derived from 5-nitrothiophene and 4-nitrobenzene with nitropropyl anion **4**. A mechanistic study of this reaction was also carried out and the data obtained proved that this reaction follows a $S_{RN}1$ mechanism. This reaction was extended to cyclic nitronates to synthesize several unknown α,β-unsaturated ketones **10-14**.

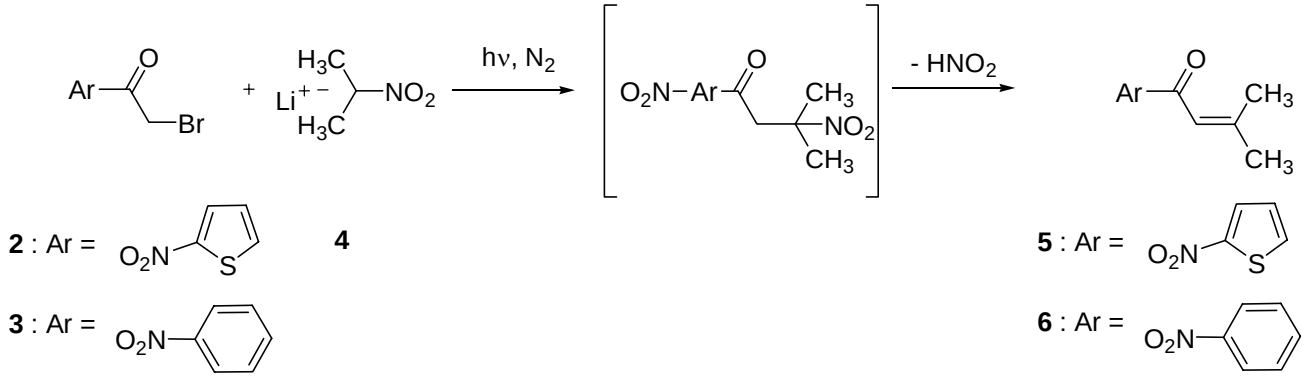
Results and Discussion

In the nitrothiophene series, the substrate 2-bromo-1-(5-nitrothiophen-2-yl)ethanone (**2**) was obtained from 1-(5-nitrothiophen-2-yl)ethanone (**1**), using a quaternary ammonium salt, tetrabutylammonium tribromide ($TBABr_3$) as brominating reagent [12] (Scheme 1). In the nitrobenzene series, the substrate 2-bromo-1-(4-nitrophenyl)ethanone (**3**) is commercially available.

Scheme 1.

The reaction of the two α-bromoketones **2** and **3** with 2–nitropropyl anion **4** was studied, under classical $S_{RN}1$ conditions (light irradiation, inert atmosphere) with several protocol variations, looking for better reaction yields. The ethylenic α,β-unsaturated ketones **5** and **6** were obtained *via* nitrous acid elimination from the *C*-alkylation intermediate (Scheme 2). Results are summarized in Table 1.

Scheme 2.



In the light of the above results, it is obvious that the best reaction condition found were: use of methanol as solvent, and two equivalents of 2-nitropropyl anion in the nitrothiophene series and three equivalents in the nitrobenzene series.

Table 1: Reaction of α-bromoketones with 2–nitropropyl anion [a].

Substrate	2-nitropropyl anion equivalents	Solvent	Product obtained	Yield (%)[b]
2	2	DMF	**5**	20
2	2	DMSO	**5**	18
2	2	MeOH	**5**	90
3	1	DMF	**6**	42
3	2	DMF	**6**	45
3	3	DMF	**6**	48
3	2	DMSO	**6**	35
3	2	MeOH	**6**	56
3	3	MeOH	**6**	63

[a] Standard conditions: the nitropropyl anion was added to the α-bromoketone with stirring under N_2, with light irradiation (2×60W tungsten lamp).

[b] Yields calculated with regards to substrates **2** or **3** based on products isolated by chromatography on silica gel and recrystallization.

The $S_{RN}1$ reaction mechanism was proved by classical mechanistic study [13], using inhibition tests by radical inhibitors, radical scavengers and the influence of light. The two bromo derivatives **2** and **3** were used as substrates, and the inhibition results obtained in each case are presented in Table 2.

Table 2: Inhibitors influence on reaction of α-bromoketones with 2–nitropropane anion [a].

Inhibitor	Yield in nitrothiophene series, 5 (%)[b]	Yield in nitrobenzene series, 6 (%)[b]
-	90	63
O_2	65	31
Dark	72	37
O_2 + Dark	58	18
TEMPO (0.1 eq.)	21	17
TEMPO (1 eq.)	13	9
p-$NO_2C_6H_4NO_2$ (0.1 eq.)	19	15
p-$NO_2C_6H_4NO_2$ (1 eq.)	8	7
$CuCl_2, 2H_2O$ (0.1 eq.)	5	5

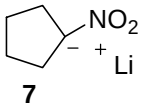
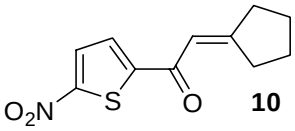
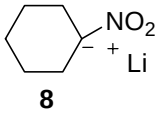
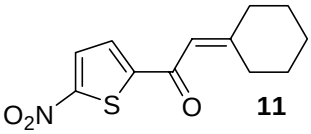
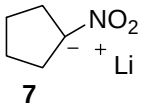
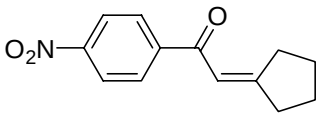
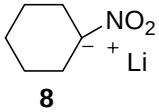
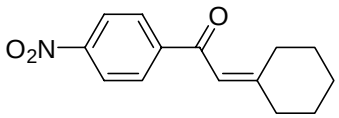
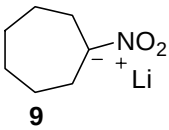
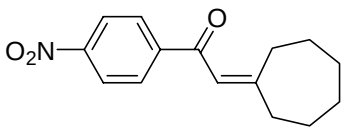
[a] Standard conditions: the nitropropyl anion was added to α-bromoketones with stirring under N_2, with light irradiation (2×60W tungsten lamp).

[b] Yields calculated with regards to substrates **2** or **3**, based on products isolated by chromatography on silica gel and recrystallization.

The yield decrease observed during these inhibition experimentas is closely related to an $S_{RN}1$ reaction involving a radical chain mechanism. Therefore, the nature of this particular reaction of α-bromoketones derived from nitrothiophene and nitrobenzene rings is confirmed.

With these simple operating conditions, generalization to other various nitronate anions is possible. Table 3 includes a few examples of the reaction with cyclic nitronate anions which afforded new α,β-unsaturated ketones.

Table 3: Generalization of $S_{RN}1$ reaction to cyclic nitronate anions [a].

Substrate	Anion	Product	Yield (%)[b]
2	 **7**	 **10**	85
2	 **8**	 **11**	70
3	 **7**	 **12**	45
3	 **8**	 **13**	48
3	 **9**	 **14**	39

[a] Standard conditions : the nitronate anion was added to α-bromoketones with stirring under N_2, with light irradiation (2×60W tungsten lamp).

[b] Yields calculated with regards to substrates **2** or **3**, based on products isolate by chromatography on silica gel and recrystallization.

In the $S_{RN}1$ literature [14], classically a mixture containing both ethylenic and *C*-alkylation nitro-substituted products was obtained from reactions of bromomethyl derivatives. Here, for bromoacetyl derivatives only ethylenic compounds were isolated, in 39% to 85% yields. This could due to the high stability of α,β-ethylenic ketones which may facilitate the nitrous acid elimination from *C*-alkylation products. Due to their structural analogy with chalcones, all the compounds prepared are currently being tested to evaluate their anticancer potential.

Acknowledgments

We are grateful to the Centre National de la Recherche Scientifique for its financial support. We also wish to express our thanks to Vincent Remusat for NMR spectra recording. Christophe Curti thanks the Université de la Méditerranée for ATER position.

Experimental

General

Melting points were determined with a B-540 Büchi melting point apparatus. ^{1}H-NMR (200 MHz) and ^{13}C-NMR (50 MHz) spectra were recorded on a Brüker ARX 200 spectrometer in $CDCl_3$ at the Service Interuniversitaire de RMN de la Faculté de Pharmacie de Marseille. ^{1}H- and ^{13}C-NMR chemical shifts (δ) are reported in parts per million with respect to the $CDCl_3$ signals at 7.26 ppm (^{1}H) and 77 ppm (^{13}C), respectively. Elemental analyses were carried out at the Centre de Microanalyses de la Faculté des Sciences et Techniques de Saint-Jérôme. The following adsorbent was used for flash column chromatography: silica gel 60 (Merck, particle size 0.063-0.200 mm, 70-230 mesh ASTM). TLC were performed on 5 cm×10 cm aluminium plates coated with silica gel 60F-254 (Merck) in appropriate solvent. Analyses were within ± 0.4% of the theoretical values.

Preparation of 2-bromo-1-(5-nitrothiophen-2-yl)ethanone using tetrabutylammonium tribromide

In a two-necked flask, a solution of **1** (0.71 g, 4.16 mmol) in dichloromethane (50 mL) and methanol (20 mL) was stirred at room temperature. Then, tetrabutylammonium tribromide (2.20 g, 4.58 mmol) was added slowly and stirring was continued for 3h. The solvent was then evaporated on a rotary evaporator and a saturated solution of sodium thiosulfate (100 mL) was added to the residue obtained. The aqueous layer was extracted with ether (4×30 mL). The combined organic layer was dried over $MgSO_4$, filtered and evaporated under vacuum. The solid residue was purified by column chromatography on silica gel eluting with chloroform. Recrystallization from cyclohexane gave **2** as a brown solid in 68% yield; mp 101 ^{o}C (from cyclohexane; Lit. 99-102 ^{o}C [15]) ^{1}H-NMR: δ 4.34 (s, 2H, CH_2), 7.70 (d, *J* = 4.3 Hz, 1H, CH), 7.91 (d, *J* = 4.3 Hz, 1H, CH); ^{13}C-NMR: δ 29.2 (CH_2), 128.2 (CH), 131.4 (CH), 130.1 (C), 144.3 (C), 184.5 (C=O).

Reaction of α-bromoketones with 2-nitropropyl anion

In a two necked flask, a solution of the corresponding α-bromoketone **2** or **3** (1.64 mmol) in DMF (5 mL), DMSO (5 mL) or methanol (10 mL) was stirred at room temperature under an inert atmosphere (N_2) and light irradiation. Appropriate quantities of the lithium salt of 2-nitropropane (**4**, one eq.: 1.64 mmol, 0.16 g; two eq.: 3.28 mmol, 0.31 g; three eq.: 4.92 mmol, 0.47 g) were added and the reaction mixture stirred for one hour. If DMF or DMSO were used as solvents, water (100 mL) was added and aqueous layer was extracted by dichloromethane (3×40 mL). The combined organic layers were washed with water (5×40 mL). In all cases, organic layer was dried over $MgSO_4$ filtered and

evaporated under vacuum. Purification by chromatography on silica gel eluting with dichloromethane in the nitrothiophene series, and with dichloromethane/petroleum ether (9/1) in the nitrobenzene series led to the corresponding products **5** in 18-90% yield and **6** in 35-63% yield after recrystallization.

3-Methyl-1-(5-nitrothiophen-2-yl)but-2-en-1-one (**5**): Yellow solid, mp 211-212 ^{o}C (cyclohexane); ^{1}H-NMR: δ 2.05 (d, *J* = 1.1 Hz, 3H, CH_3), 2.27 (d, *J* = 1.1 Hz, 3H, CH_3), 6.62 (m, 1H, CH), 7.55 (d, *J* = 4.3 Hz, 1H, CH), 7.86 (d, *J* = 4.3 Hz, 1H, CH); ^{13}C-NMR: δ 19.0 (CH_3), 21.6 (CH_3), 118.6 (CH), 128.3 (CH), 128.4 (CH), 147.1 (C), 151.1 (C), 162.2 (C), 182.0 (C=O); Anal. Calcd for $C_9H_9NO_3S$: C, 51.17; H, 4.29; N, 6.63. Found C, 51.38; H, 4.21; N, 6.51.

3-Methyl-1-(4-nitrophenyl)but-2-en-1-one (**6**): Yellow solid, mp 104 ^{o}C (isopropanol; Lit. 103-106 ^{o}C [11]); ^{1}H-NMR: δ 2.05 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 6.75 (s, 1H, CH), 8.17 (d, *J* = 8.9 Hz, 2H, 2CH), 8.36 (d, *J* = 8.9 Hz, 2H, 2CH); ^{13}C-NMR: δ 21.4 (CH_3), 28.1 (CH_3), 120.2 (CH), 123.6 (2CH), 128.9 (2CH), 144.0 (C), 149.6 (C), 160.3 (C), 189.1 (C=O); Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found C, 64.19; H, 5.40; N, 6.71.

Mechanistic study of the reaction between α-bromoketones and 2-nitropropyl anion

All these reactions were peeformed following the previous protocols, in methanol (10 mL), using two equivalents of nitropropyl anion in the nitrothiophene series and three equivalents in the nitrobenzene series.

Generalization of $S_{RN}1$ reaction of α-bromoketones with other nitronate anions.

Lithium salts of cyclic nitronate anions were used instead of the 2-nitropropyl anion following the same general procedure of the reaction between α-bromoketones and 2-nitropropane anion in methanol. In the case of nitrothiophene series, two equivalents of the cyclic nitronate were used: lithium salt of nitrocyclopentane **7** (3.28 mmol, 0.40 g) or of nitrocyclohexane **8** (3.28 mmol, 0.44 g). In the nitrobenzene series, three equivalents of the cyclic nitronate were used: lithium salt of nitrocyclopentane **7** (4.92 mmol, 0.60 g), nitrocyclohexane **8** (4.92 mmol, 0.66 g), or nitrocycloheptane **9** (4.92 mmol, 0.74 g). Purification by chromatography on silica gel eluting with dichloromethane in the nitrothiophene series, and with dichloromethane/petroleum ether (9/1) in the nitrobenzene series led to the corresponding products **10-14** after recrystallization.

2-Cyclopentylidene-1-(5-nitrothiophen-2-yl)ethanone (**10**): 85% yield; yellow solid, mp 227 ^{o}C (cyclohexane); ^{1}H-NMR: δ 1.79 (m, 4H, $2CH_2$), 2.62 (m, 2H, CH_2), 2.91 (m, 2H, CH_2), 6.83 (s, 1H, CH), 7.55 (d, *J* = 4.3 Hz, 1H, CH), 7.88 (d, *J* = 4.3 Hz, 1H, CH); ^{13}C-NMR: δ 26.1 (CH_2), 28.9 (CH_2), 30.9 (CH_2), 38.7 (CH_2), 115.9 (CH), 128.5 (CH), 128.4 (CH), 147.1 (C), 151.1 (C), 162.2 (C), 182.7 (C=O); Anal. Calcd for $C_{11}H_{11}NO_3S$: C, 55.68; H, 4.67; N, 5.90. Found C, 55.34; H, 4.71; N, 5.98.

2-Cyclohexylidene-1-(5-nitrothiophen-2-yl)ethanone (**11**): 70% yield; yellow solid, mp 240 ^{o}C (cyclohexane); ^{1}H-NMR: δ 1.67 (m, 6H, $3CH_2$), 2.33 (m, 2H, CH_2), 2.90 (m, 2H, CH_2), 6.52 (s, 1H),

7.56 (d, *J* = 4.3 Hz, 1H, CH), 7.87 (d, *J* = 4.3 Hz, 1H, CH), ^{13}C-NMR: δ 26.0 (CH_2), 28.0 (CH_2), 28.8 (CH_2), 30.8 (CH_2), 38.7 (CH_2), 115.9 (CH), 128.4 (CH), 128.5 (CH), 147.0 (C), 151.2 (C), 169.0 (C), 182.7 (C=O); Anal. Calcd for $C_{12}H_{13}NO_3S$: C, 57.35; H, 5.21; N, 5.57. Found C, 57.01; H, 5.32; N, 5.41.

2-Cyclopentylidene-1-(4-nitrophenyl)ethanone (**12**): 45% yield; yellow solid, mp 120 ^{o}C (isopropanol); ^{1}H-NMR: δ 1.79 (m, 4H, $2CH_2$), 2.60 (m, 2H, CH_2), 2.90 (m, 2H, CH_2), 7.00 (s, 1H, CH), 8.05 (d, *J* = 8.9 Hz, 2H, 2CH), 8.29 (d, *J* = 8.9 Hz, 2H, 2CH); ^{13}C-NMR: δ 25.3 (CH_2), 26.5 (CH_2), 34.4 (CH_2), 37.1 (CH_2), 115.2 (CH), 124.2 (2CH), 128.3 (2CH), 144.2 (C), 150.1 (C), 175.0 (C), 188.4 (C=O); Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found C, 67.68; H, 5.73; N, 6.09.

2-Cyclohexylidene-1-(4-nitrophenyl)ethanone (**13**): 48% yield; yellow solid, mp 136 ^{o}C (isopropanol); ^{1}H-NMR: δ 1.64 (m, 6H, $3CH_2$), 2.32 (m, 2H, CH_2), 2.79 (m, 2H, CH_2), 6.59 (s, 1H, CH), 8.03 (d, *J* = 8.9 Hz, 2H, 2CH), 8.25 (d, *J* = 8.9 Hz, 2H, 2CH); ^{13}C-NMR: δ 26.0 (CH_2), 27.9 (CH_2), 28.8 (CH_2), 30.7 (CH_2), 38.5 (CH_2), 117.7 (CH), 123.8 (2CH), 129.0 (2CH), 144.0 (C), 149.6 (C), 166.6 (C), 189.9 (C=O); Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found C, 68.08; H, 6.07; N, 5.89.

2-Cycloheptylidene-1-(4-nitrophenyl)ethanone (**14**): 39% yield; yellow solid, mp 88 ^{o}C (isopropanol); ^{1}H-NMR: δ 1.70 (m, 8H, $4CH_2$), 2.54 (m, 2H, CH_2), 2.97 (m, 2H, CH_2), 6.76 (s, 1H, CH), 8.05 (d, *J* = 8.9 Hz, 2H, 2CH), 8.27 (d, *J* = 8.9 Hz, 2H, 2CH); ^{13}C-NMR: δ 26.4 (CH_2), 28.1 (CH_2), 29.2 (CH_2), 29.8 (CH_2), 33.8 (CH_2), 39.8 (CH_2), 119.5 (CH), 123.6 (2CH), 128.9 (2CH), 144.4 (C), 149.6 (C), 171.6 (C), 189.0 (C=O); Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found C, 69.13; H, 6.77; N, 5.32.

References

1. Marzinzik, A.L.; Felder, E.R. Key Intermediates in Combinatorial Chemistry: Access to Various Heterocycles from α,β-unsaturated ketones on Solid Phase, *J. Org. Chem.* **1998**, *63*, 723-727.
2. Srikanth, G.S.C.; Castle, S.L. Advances in radical conjugate additions, *Tetrahedron* **2005**, *61*, 10377-10441.
3. Furusawa, M.; Tanaka; T.; Ito, T.; Nishiwaka, A.; Yamazaki, N.; Nakaya, K.I.; Matsuura, N.; Tsuchiya, H.; Nagayama, M.; Iinuma, M. Antioxidant Activity of Hydroxyflavonoids**,** *J. Health Sci.* **2005**, *51*, 376-378.
4. Dimmock, J.R.; Jha, A.; Zello, G.A. ; Quail, J.W. ; Oloo, E.O. ; Nienaber, K.H. ; Kowalczyk, E.S.; Allen, T.M.; Santos, C.L.; De Clerck, E.; Balzarini, J.; Manavathu, E.K.; Stables, J.P. Cytotoxic *N*-[4-(3-aryl-3-oxo-1-propenyl)phenylcarbonyl]-3,5-bis(phenylmethylene)-4-piperidones and related compounds, *Eur. J. Med. Chem.* **2002**, *37*, 961-972.
5. Nam, N.H.; Hong, D.H.; You, Y.J.; Kim, Y.; Bang, S.C.; Kim, H.M.; Ahn, B.Z. Synthesis and cytotoxicity of 2,5-dihydroxychalcones and related compounds, *Arch. Pharm. Res.* **2004**, *27*, 581-588.

6. Yayli, N.; Goek, Y.; Uecuencue, O.; Yasar, A.; Atasoy, C.; Sahinbas, E.; Kuecuek, M. Stereoselective photochemistry of substituted chalcones in solution and their antioxidant activities, *J. Chem. Res.* **2005**, *3*, 155-159.
7. Bardia, R.; Rao, J.T. Synthesis and antimicrobial activity of some α,β-unsaturated aromatic ketones, *Asian J. Chem.* **2004**, *16*, 1194-1196.
8. Remusat, V.; Terme, T.; Gellis, A.; Rathelot, P.; Vanelle, P. Synthesis of original benzo[*g*]quinoxaline-5,10-diones by bis-$S_{RN}1$ methodology, *J. Heterocycl. Chem.* **2004**, *41*, 221-225.
9. Njoya, Y.; Gellis, A.; Crozet, M.P.; Vanelle, P. Efficient synthesis of new 6-nitrobenzothiazoles using microwave irradiation, *Sulfur Lett.* **2003**, *26*, 67-75.
10. Vanelle, P.; Gellis, A.; Kaafarani, M.; Maldonado, J.; Crozet, M.P. Fast electron transfer *C*-alkylation of 2-nitropropane anion under microwave irradiation, *Tetrahedron Lett.* **1999**, *40*, 4343-4346.
11. Russell, G.A.; Ros, F. Electron transfer processes. 34. Reactions of α-haloketones with Nucleophiles, *J. Am. Chem. Soc.* **1985**, *107*, 2506-2511.
12. Kajigaeshi, S.; Kakinami, T. ; Okamoto, T.; Fujisaki, S. Synthesis of bromoacetyl derivatives by use of tetrabutylammonium tribromide, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1159-1160.
13. Chanon, M.; Tobe, M.L. ETC: A Mechanistic Concept for Inorganic and Organic Chemistry, *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 1-23.
14. Vanelle, P., Ed.; *Electron Transfer Reactions in Organic Synthesis*; Research Signpost: Trivandrum, **2002** and references therein.
15. Deady, L.W., Stanborough, M.S. The synthesis of 2-(heteroaryl)imidazo[1,2-*a*]pyridin-3-ols and related compounds, *Aust. J. Chem.* **1981**, *34*, 1295-1302.

Sample Availability: Not available.