EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 3
Issue: 7
416-420
Year: 2016

SYNTHESIS OF NEW FLUORINATED PYRROLE DERIVATIVES USING PAAL-KNORR CONDENSATION

Murtaza A. Patharia*[a] , Pankaj K. Godhaviya[a] Bharat K. Dhotre[b] Pathan Mohd Arif[c]

[a]Navin Research and Innovation Centre, NFIL Surat, Gujarat, India.
[b]Department of Chemistry, Swami vivekanand Senior College Mantha, Maharashtra, India.
[c]Department of Chemistry, Maulana Azad College Aurangabad, Maharashtra, India.

Corresponding Author: Murtaza A. Patharia
Navin Research and Innovation Centre, NFIL Surat, Gujarat, India.

Article Received on 06/05/2016 **Article Revised on 27/05/2016** **Article Accepted on 16/06/2016**

ABSTRACT
The paper constitutes the research performed to developed new fluorinated pyrrole derivatives by Paal-Knorr condensation reaction of respective amino fluorinated compounds in suitable non-polar aprotic solvent. The reaction is clean which enable to easy workup and good yield.

KEYWORDS: Fluorinated benzoic acid, Fluorinated amines, Pall-Knorr condensation.

INTRODUCTION

Fluorinated pyrrole compounds which may be useful in medicinal field. Since fluorine atom possesses high electronegativity it has hydrophilic character. Also C-F bond is much stronger than C-H which increases the bioavailability and half-life of the compounds.

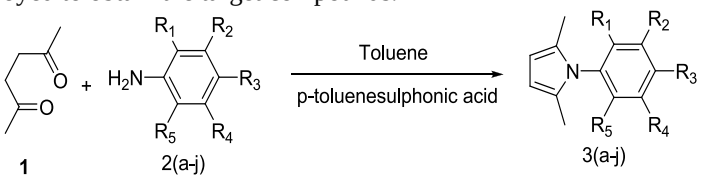
It is well known that $-CF_3$ group plays important role in medicinal chemistry as it enhances the efficacy by promoting electrostatic interaction with targets, improving cellular membrane permeability and increasing resistance towards oxidative metabolism of the drug.

Also, new fluoro-substituted analogs are currently being designed with the aim of increasing metabolic stability of the molecule. As it is known in the literature, the incorporation of fluorine enhances therapeutic efficacy and improves pharmacological properties in bioactive molecules. The presence of fluorine often leads to increased lipid solubility, enhancing rates of absorption and transport of drugs in vivo.

Pyrrole derivatives are having significant synthetic importance due to their extensive use in drug discovery[1] and also for pharmacological activity such as anti-inflammatory[2], cytotoxicity[3,4], in vitro cytotoxic activity against solid tumor model[5,6], treatment of hyperlipidemias[7], and antitumor agents.[8]. The pyrrole containing heterocyclic derivatives have been reported in synthetic and effective biological importance.[9,10] Pyrrole derivatives have biological activity such as COX-1/COX-2 inhibitors[11] and cytotoxic activity against a variety of marine and human tumor models,[12]

Reaction scheme

The synthesis scheme employed to obtain the target compounds.



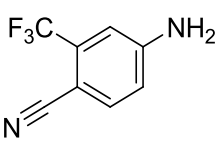
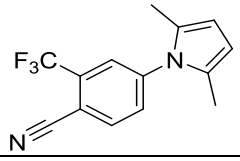
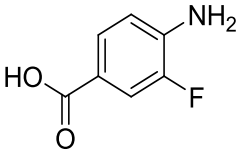
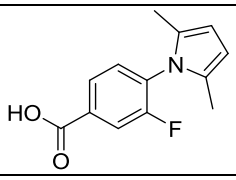
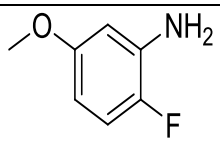
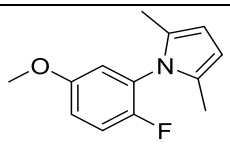
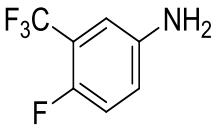
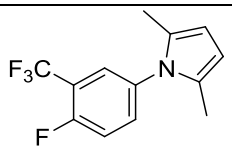
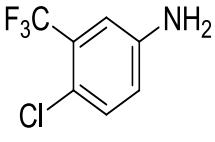
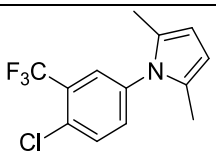
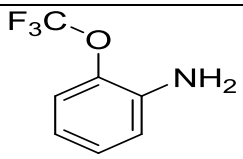
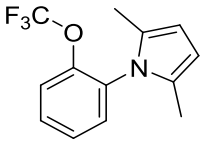
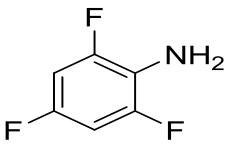
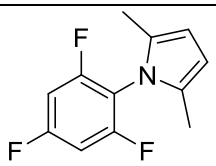
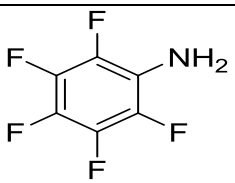
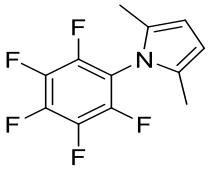
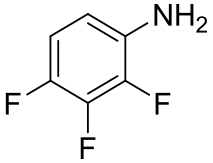
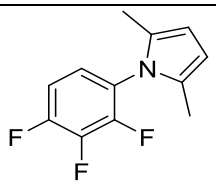
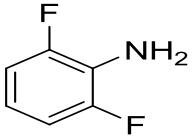
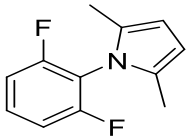
where R_1, R_2 = -COOH, -CN, $-CF_3$, -F, -Cl, -H, $-OCH_3$, $-OCF_3$

Scheme-1 reagents and condition: **(**1) Acetonyl acetone 1.05 Eq, dry toluene, catalytic amount of p-toluenesulphonic acid 0.5%w/w, 3-4hr reflux.

Pyrrole derivatives 3(a-j) are synthesized by the reaction of different substituted aniline 2(a-j) with acetonyl acetone in presence of catalytical amount of p-toluenesulphonic acid using non-polar solvent at reflux temperature to get the desired compounds in pure form as reaction is clean and performed in mole to mole ratio with conditions employed which minimize the impurities.[13-16]

RESULTS AND DISCUSSION

Table-1 Pyrrole derivatives

Entry	Aniline	Product	Time (h)	Yield (%)	MP (^{0}C)
a			8	88	85-89
b			7	85	148-150
c			9	90	Oil
d			9	91	85-88
e			12	81	94-97
f			8	83	Oil
g			10	82	111-113
h			12	79	72-75
i			10	84	103-106
j			9	78	124-127

CONCLUSION

The process for the synthesis of pyrrole derivatives is relatively simpler. The reagents used are also available commercially and easy to handle. Also the process is easily scalable and commercially feasible as all the compounds are synthesize in good yields. The

synthesized compounds are characterized by Mass and IR spectra and 1HNMR.

EXPERIMENTAL SECTION

General. All starting materials and solvents were purchased from common commercial suppliers and were used freshly purified by standard procedures if required. Reactions were monitored by TLC using silica-gel coated plates and ethyl acetate/hexanes solutions as the mobile phase, spots were located by iodine and UV. FT-IR spectra were recorded using KBr disks on a Bruker Vector-22 infrared spectrometer and absorptions are reported as wave numbers (cm-1). ^{1}H NMR spectra were obtained on a FT-NMR Bruker Ultra ShieldTM (400 MHz) instrument as DMSO-d_6 solutions and the chemical shifts are expressed as units with Me_4Si as the internal standard. Mass spectra were recorded on direct inlet probe on a GCMS-QP 2010 mass spectrometer (Shimadzu). Elemental analyses were performed using a Thermo Finnigan Flash EA 1112 instrument.

General procedure for synthesis of Pyrrole derivatives [3(a-j)]

Fluorinated amines 2(a-j) was dissolve in fresh anhydrous toluene (5.0Volumes) and p-toluenesulphonic acid (0.5%w/w) was added at 25-35^{o}C. Acetonyl acetone (1.05Eq) was added dropwise to the reaction mixture. Then reaction mixture was heated at reflux temperature using dean stark apparatus. Once the water distillation stopped then the reaction was monitored by TLC to check the completion. After reaction completion, the reaction mass was cooled to room temperature and washed with water. Organic layer was dried upon Na_2SO_4, filter through cotton and was distilled under reduce pressure to obtained desire compound.

1. 4-(2,5-dimethyl-1H-pyrrol-1-yl)-3-(trifluoromethyl)benzonitrile (3a)

^{1}H NMR (400 MHz, DMSO): δ= 7.98 (d, J = 1.8 Hz, 1H), 7.68 (dd, J = 7.8 Hz, J = 2.0 Hz, 1H), 7.43 (dd, J = 7.9 Hz, J = 0.8 Hz, 1H), 5.86 (s, 2H), 2.00 (s, 6H); Yield: 88%; mp: 85-89 ^{o}C; IR (cm^{-1}): 3036 (C-H aromatic ring), 2918 (C-H), 2856 (C-H), 2240 (C=N), 1585 (C=N), 1464 (C=C), 1337 (C-H), 1308 (C-H), 1263 (C-N), 1008 (C-F) cm^{-1}. MS (m/z): 264 (M+); Anal. calcd for $C_{14}H_{11}F_3N_2$: C, 63.63; H, 4.20; F, 21.57; N, 10.60; Found: C, 63.57; H, 4.12; F, 21.48; N, 10.51.

2. 4-(2,5-dimethyl-1H-prrol-1-yl)-3-fluorobenzoic acid (3b)

^{1}H NMR (400 MHz, DMSO): δ= 10.78 (s, 1H), 7.81 (dd, J = 8.3 Hz, J = 2.3 Hz, 1H), 7.58 (dd, J = 8.0Hz, J = 1.2 Hz, 1H), 7.40 (dd, J = 8.0 Hz, J = 1.5 Hz, 1H), 5.86 (s, 2H), 1.99 (s, 6H); Yield: 85%; mp: 148-150 ^{o}C; IR (cm^{-1}): 3109 (COO-H), 3043 (C-H aromatic ring), 2945 (C-H), 2832 (C-H), 1710 (C=O), 1566 (C=N), 1468 (C=C), 1355 (C-H), 1327 (C-H), 1257 (C-N), 1017 (C-F) cm^{-1}. MS (m/z): 233 (M+); Anal. calcd for $C_{13}H_{12}FNO_2$: C, 66.94; H, 5.19; F, 8.15; N, 6.01; O, 13.72; Found: C, 66.74; H, 5.27; F, 8.06; N, 6.04; O, 13.61.

3. 1-(2-fluoro-5-methoxyphenyl)-2,5-dimethyl-1H-pyrrole (3c)

Yield: 90%; Oily compound; IR (cm^{-1}): 3018 (C-H aromatic ring), 2989 (C-H), 2878 (C-H), 1559 (N-O), 1528 (C=N), 1432 (C=C), 1348 (C-H), 1327 (C-H), 1269 (C-N), 1021 (C-F) cm^{-1}. MS (m/z): 219 (M+); Anal. calcd for $C_{13}H_{14}FNO$: C, 71.21; H, 6.44; F, 8.66; N, 6.39; O, 7.30; Found: C, 71.14; H, 6.32; F, 8.51; N, 6.28; O, 7.24.

4. 1-(4-fluoro-3-(trifluoromethyl)phenyl)-2,5-dimethyl-1H-pyrrole (3d)

Yield: 91%; mp: 85-88 ^{o}C; IR (cm^{-1}): 3052 (C-H aromatic ring), 2910 (C-H), 2847 (C-H), 1525 (C=N), 1429 (C=C), 1316 (C-H), 1306 (C-H), 1284 (C-N), 1023 (C-F) cm^{-1}. MS (m/z): 257 (M+); Anal. calcd for $C_{13}H_{11}F_4N$: C, 60.70; H, 4.31; F, 29.54; N, 5.45; Found: C, 60.21; H, 4.15; F, 29.38; N, 5.09.

5. 1-(4-chloro-3-(trifluoromethyl)phenyl)-2,5-dimethyl-1H-pyrrole (3e)

Yield: 81%; mp: 94-97 ^{o}C; IR (cm^{-1}): 3028 (C-H aromatic ring), 2915 (C-H), 2832 (C-H), 1549 (C=N), 1436 (C=C), 1319 (C-H), 1302 (C-H), 1263 (C-N), 1017 (C-F), 605 (C-Cl) cm^{-1}. MS (m/z): 273 (M+); Anal. calcd for $C_{13}H_{11}ClF_3N$: C, 57.05; H, 4.05; Cl, 12.95; F, 20.83; N, 5.12; Found: C, 57.02; H, 4.10; Cl, 12.76; F, 20.68; N, 5.06.

6. 2,5-dimethyl-1-(2-(trifluoromethoxy)phenyl)-1H-pyrrole (3f)

Yield: 83%; Oily compound; IR (cm^{-1}): 3082 (C-H aromatic ring), 2943 (C-H), 2830 (C-H), 1585 (C=N), 1423 (C=C), 1348 (C-H), 1317 (C-H), 1278 (C-N), 1186 (C-O), 1023 (C-F) cm^{-1}. MS (m/z): 255 (M+); Anal. calcd for $C_{13}H_{12}F_3NO$: C, 61.17; H, 4.74; F, 22.33; N, 5.49, O, 6.27; Found: C, 61.12; H, 4.68; F, 22.24; N, 5.37, O, 6.18.

7. 2,5-dimethyl-1-(2,4,6-trifluorophenyl)-1H-pyrrole (3g)

Yield: 82%; mp: 111-113 ^{o}C; IR (cm^{-1}): 3045 (C-H aromatic ring), 2949 (C-H), 2821 (C-H), 1532 (C=N), 1454 (C=C), 1346 (C-H), 1324 (C-H), 1258 (C-N), 1012 (C-F) cm^{-1}. MS (m/z): 225 (M+); Anal. calcd for $C_{12}H_{10}F_3N$: C, 64.00; H, 4.48; F, 25.31; N, 6.22; Found: C, 64.00; H, 4.39; F, 25.19; N, 6.14.

8. 2,5-dimethyl-1-(pentafluorophenyl)-1H-pyrrole (3h)

Yield: 79%; mp: 72-75 ^{o}C; ^{1}H NMR (400 MHz, DMSO): δ= 5.87 (s, 2H), 1.98 (s, 6H); IR (cm^{-1}): 3036 (C-H aromatic ring), 2932 (C-H), 2831 (C-H), 1568 (C=N), 1461 (C=C), 1381 (C-H), 1355 (C-H), 1278 (C-N), 1002 (C-F) cm^{-1}. MS (m/z): 261 (M+); Anal. calcd for $C_{12}H_8F_5N$: C, 55.18; H, 3.09; F, 36.37; N, 5.36; Found: C, 55.12; H, 3.04; F, 36.31; N, 5.28.

9. 2,5-dimethyl-1-(2,3,4-trifluorophenyl)-1H-pyrrole (3i)

Yield: 84%; mp: 103-106 ^{o}C; IR (cm^{-1}): 3078 (C-H aromatic ring), 2954 (C-H), 2837 (C-H), 1534 (C=N), 1462 (C=C), 1348 (C-H), 1321 (C-H), 1269 (C-N), 1018 (C-F) cm^{-1}. MS (m/z): 225 (M+); Anal. calcd for $C_{12}H_{10}F_3N$: C, 64.00; H, 4.48; F, 25.31; N, 6.22; Found: C, 64.02; H, 4.34; F, 25.27; N, 6.17.

10. 1-(2,6-difluorophenyl)-2,5-dimethyl-1H-pyrrole (3j)

Yield: 78%; mp: 124-127 ^{o}C; IR (cm^{-1}): 3069 (C-H aromatic ring), 2956 (C-H), 2825 (C-H), 1523 (C=N), 1486 (C=C), 1368 (C-H), 1354 (C-H), 1263 (C-N), 1008 (C-F) cm^{-1}. MS (m/z): 207 (M^+); Anal. calcd for $C_{12}H_{11}F_2N$: C, 69.55; H, 5.35; F, 18.34; N, 6.76; Found: C, 69.32; H, 5.27; F, 18.22; N, 6.68.

BIOLOGICAL ACTIVITY

Pharmacology

The minimum inhibitory concentrations (MICs) of synthesized compounds were carried out by broth microdilution method as described by Rattan Antibacterial activity was screened against two gram positive (Staphylococcus aureus MTCC 96, Streptococcus pyogenus MTCC 443) and two gram negative (Escherichia coli MTCC 442, Pseudomonas aeruginosa MTCC 441) bacteria, ampicillin was used as a standard antibacterial agent. Antifungal activity was screened against three fungal species Candida albicans MTCC 227, Aspergillus niger MTCC 282 and Aspergillus clavatus MTCC 1323, Griseofulvin was used as a standard antifungal agent.

All MTCC cultures were collected from Institute of Microbial Technology, Chandigarh and Mueller Hinton broth was used as nutrient media to grow and diluted the drug suspension for the test. Inoculum size for test strain was adjusted to 108 CFU (Colony Forming Unit) per milliliter by comparing the turbidity. DMSO was used to dilute to get desired concentration of drugs to test upon standard bacterial strains. Serial dilutions were prepared in primary and secondary screening. The control tube containing no antibiotic was immediately sub cultured (before inoculation) by spreading a loopful evenly over a quarter of plate of medium suitable for the growth of the test organism and put for incubation at 37 °C overnight. The tubes were then incubated overnight. The MIC of the control organism was read to check the accuracy of the drug concentrations. The lowest concentration inhibiting growth of the organism was recorded as the MIC. All the tubes not showing visible growth (in the same manner as control tube described above) were sub cultured and incubated overnight at 37 °C. The amount of growth from the control tube before incubation (which represents the original inoculum) was compared. Subcultures might show similar number of colonies indicating bacteriostatic; a reduced number of colonies indicating a partial or slow bactericidal activity and no growth if the whole inoculum has been killed. The test must include a second set of the same dilutions inoculated with an organism of known sensitivity. Each synthesized drug was diluted for obtaining 2000 µg/ml concentration, as a stock solution. In primary screening 500 µg/ml, 250µg/ml and 125 µg/ml concentrations of the synthesized drugs were taken. The active synthesized drugs found in this primary screening were further tested in a second set of dilution against all microorganisms. The drugs found active in primary screening were similarly diluted to obtain 100 µg/ml, 50 µg/ml, 25 µg/ml, 12.5 µg/ml, 6.25 µg/ml, 3.12 µg/ml and 1.56 µg/ml concentrations. The highest dilution showing at least 99 % inhibition is taken as MIC. Results obtained are given in Table 1.

Antibacterial activity

The minimum inhibitory concentrations (MICs) of the tested compounds are shown in Table 1. The different compounds 3(a-j) were tested for in vitro against two gram positive (S. aureus MTCC 96, S. pyogenus MTCC 443) and two gram negative (E. coli MTCC 442, P. aeruginosa MTCC 441) bacteria. From the screening data, some of them possessed excellent antibacterial activity compared to ampicillin (MBC, 50-250 µg/ml) against gram positive S. aureus. Compounds 3a, 3e and 3i showed MBC value in the range between 62.5-100 µg/ml while ampicillin has standard MBC value of 100 µg/ml against gram negative E. coli which indicates that this compounds have excellent activity, while compounds 3d, 3f and 3h displayed moderate activity in the range of 200-250 µg/ml against gram negative E. coli compare to ampiciline. Compounds 3d and 3g exhibited very good activity against P. aeruginosa, while compounds 3a, 3h and 3j displayed moderate activity in the range of 200-250 µg/ml. Compound 3d showed MBC value in the range between 62.5-100 µg/ml against S. aureus while ampicillin has standard MBC value of 100 µg/ml against S. aureus which indicates that this compounds have excellent activity, while other compounds 3a, 3c, 3e and 3g possessed MBC value in the range of 200-250 µg/ml against against gram positive S. aureus compared with ampicillin. Compound 3h have MBC of 100 µg/ml which was comparatively good against S. pyogenus while compounds 3c, 3e, 3f and 3i displayed moderate activity in the range of 200-250 µg/ml against S. pyogenus as compare to ampiciline. The remaining Pyrrole derivatives possessed moderate to poor activity against all four bacterial species.

Antifungal activity

The minimum inhibitory concentrations (MICs) of the synthesized compounds are shown in Table 1. For in vitro antifungal activity, three fungal species C, albicans MTCC 227, A. niger MTCC 282 and A. clavatus MTCC 1323 were used and compared with standard drugs nystatin and greseofulvin. Most of the compounds possessed very good antifungal activity against A. niger; their MFC values were in the range between 100-500 µg/ml. Compounds 3e and 3h possesses good activity of 250 µg/ml against C. albicans, compounds 3c, 3e and 3i

showed excellent activity of 100-250 µg/ml which is similar to griseofulvin (100 µg/ml) and nystatin (100 µg/ml) against A. niger, while compounds 3a and 3c possesses good activity of 200-250 µg/ml against A. clavatus. whereas remaining compounds possessed moderate to poor activity against C. albicans and A. clavatus compared with griseofulvin.

Table-1: in vitro Antimicrobial Screening Results for 3a to 3j

Code	Minimal inhibition concentration (µg mL^{-1})						
	Gram-positive		Gram-negative		Fungal species		
	S.aureus	S.pyogenus	E.coli	P.aeruginosa	C.albicans	A.niger	A.clavatus
3a	200	450	**100**	200	450	500	200
3b	500	450	500	900	>1000	550	550
3c	200	250	450	450	450	200	250
3d	**100**	450	200	**100**	500	>1000	900
3e	250	200	**100**	450	250	**100**	500
3f	450	200	250	900	1000	500	450
3g	250	450	500	**100**	>1000	550	550
3h	450	**100**	250	250	250	450	>1000
3i	500	250	**62.5**	450	450	**100**	500
3j	900	450	1000	250	500	450	>1000
Gentamycin	0.25	0.5	0.05	1	-	-	-
Ampicillin	250	100	100	100	-	-	-
Chloramphenicol	50	50	50	50	-	-	-
Iprofloxacin	50	50	25	25	-	-	-
Norfloxacin	10	10	10	10	-	-	-
Nystatin	-	-	-	-	100	100	100
Greseofulvin	-	-	-	-	500	100	100

REFERENCES

1. E. Toja; A. Depaoli; G. Tuan; J. Kettenring, Synthesis, 1987; 272.
2. M. Josheph; H. Muchowski Stefan; T. Unger; J. Ackrell; P. Cheung; F. Gray; C.J. Cook; J. Med. Chem., 1985; 28: 1037.
3. G. Dannhardt; W. Kiefer; G. Karmer; S. Maehrlein; U. Nowe; B. Fiebich; Eur. J. Med. Chem., 2000; 35: 499.
4. I.K. Khanna; R.M. Weier; Y. Yu; P.W. Collins; J.M. Miyashiro; C.M. Koboldt; A.W. Veenhuizen; J.L. Currie; K. Seibert; P.C. Isakson; J. Med. Chem., 1997; 40: 1616.
5. B.S. Burnham; J.T. Gupton; K.E. Krumpe; T. Webb; J. Shuford; B. Bowers; A.E. Warren; C. Barnes; I.H. Hall; Arch. Pharm. Pharm. Med. Chem., 1998; 331: 337.
6. J.T. Gupton; B.S. Burnham; B.D. Byrd; K.E. Krumpe; C. Stokes; J. Shuford; S. Winkle; T. Webb; A.E. Warren; C. Barnes; J. Henry; I.H. Hall; Pharmazie, 1999; 54: 691.
7. M.H. Justin; K. O'Toole-Colin; A. Getzel; A. Argenti; A. Michael; Molecules, 2004; 9: 135.
8. K. Krowicki; T. Jan Balzarini; Krik De Clercq; A. Robert Newman; J. WilliamLawn; J. Med. Chem., 1988; 31: 341.
9. A.M. Almerico; P. Diana; P. Barraja; G. Dattolo; F. Mingoia; A.G. Loi; F. Scintu; C. Milia; I. Puddu; P. La Colla; Farmaco, 1998; 53: 33.
10. H. Carpio; E. Galeazzi; R. Greenhouse; A. Guzman, E. Velarde; Y. Antonio; Can. J. Chem., 1982; 60: 2295.
11. D.T. Dannhar; G. Kiefer; W. Karmer; G. Maehrlein; S. Nowe; U. Fiebich; Eur. J. Med. Chem., 2000; 35: 499.
12. M.A. Evans; D.C. Smith; J.M. Holub; A. Argenti; M. Hoff; G.A. Dalglish; Arch. Pharm. Pharm. Med. Chem., 2003; 336: 181.
13. Osadnik, Andreas; Lutzen, Arne; Arkivoc, 2014; 2015: 40-51.
14. Sinha, Mantosh K.; Reany, Ofer; Pavari, Galit; Karmakar, Ananta; Keinan, Ehud; Chemistry-A European journal, 2010; 16: 9056-9067.
15. Albrecht, Markus; Song, Yun; Synthesis, 2006; 18: 3037-3042.
16. Walia Amit, Kang, Soosung; Silverman, Richard B; Journal of Organic chemistry, 2013; 78: 10931-10937.