Research Article ISSN 2832-9384

Journal of Materials and Polymer Science

Solid Phase Ball-Milling Procedure for the Synthesis of Some New N-Biphenyl-Acetylene Substituted Heterocycles and Their Potential Anticancer Activities

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Submitted: 17 Jan 2026; Accepted: 23 Jan 2026; Published: 16 Feb 2026

Citation: Chakraborty, B. et al. (2026). Solid Phase Ball-Milling Procedure for the Synthesis of Some New N-Biphenyl-Acetylene Substituted Heterocycles and Their Potential Anticancer Activities. *J mate poly sci, 6*(1) :1-7. DOI : https://doi.org/10.47485/2832-9384.1081

Abstract

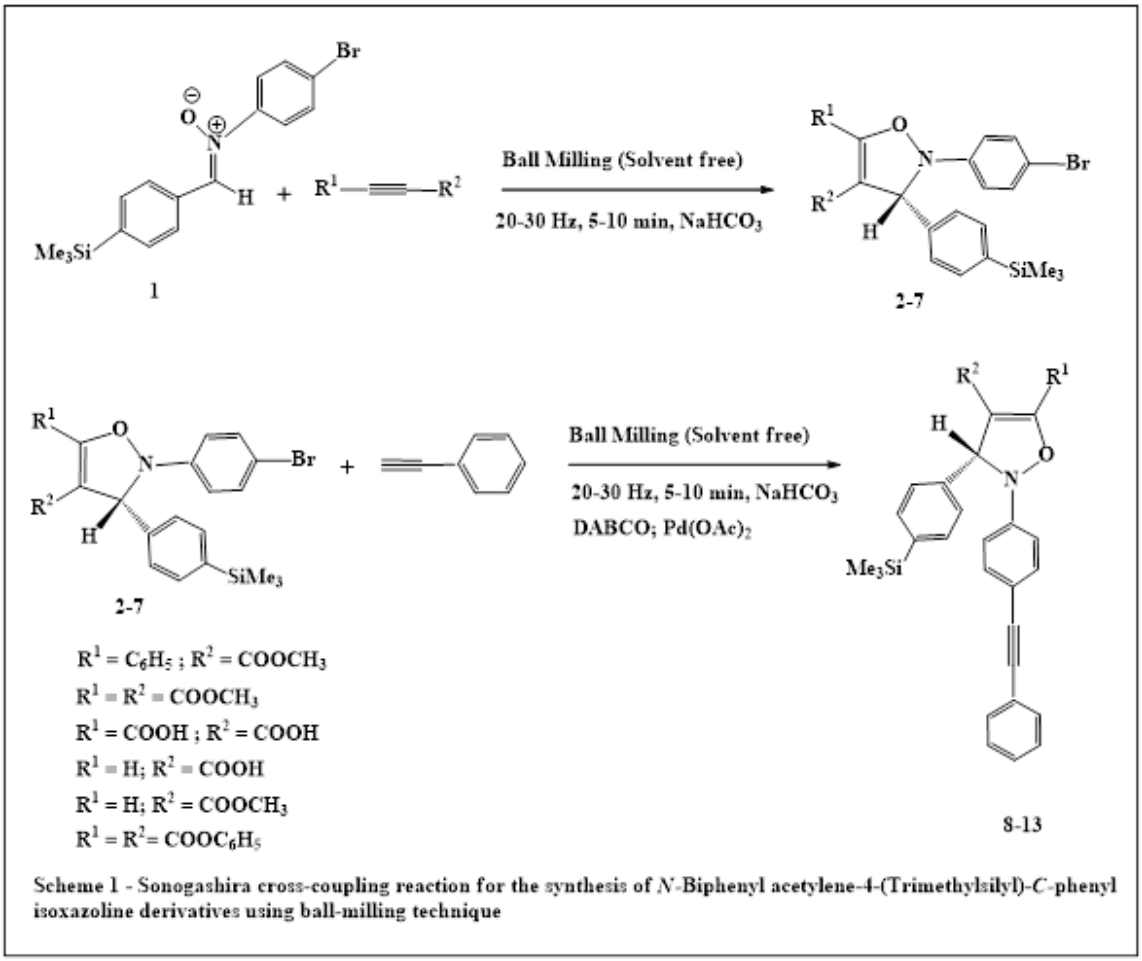
Solvent free ball-milling procedure using Sonogashira cross-coupling reaction has been employed successfully for the synthesis of some new N-Biphenyl acetylene substituted heterocyclic molecules. The starting materials, N-4-Bromo-phenyl-4-(Trimethylsilyl)-C-phenyl isoxazoline derivatives have been synthesized from N-4-Bromo-phenyl-4-(Trimethylsilyl)-C-phenyl nitrones and employed in this syntheses. This approach not only make our research work cost-efficient but also follows one of the primary protocols of green chemistry principals (atom efficient reaction). The use of sodium bicarbonate as solid support in the ball-milling procedure enhances the reaction rates as well as yields of the new heterocyclic molecules to a great extent. We have also conducted preliminary screening of these cross-coupling molecules for cancer cell studies and found significant outcomes.

Keywords: Sonogashira cross-coupling reaction, Trimethyl silyl isoxazoline derivative, atom efficient reaction, anticancer study

Introduction

Sonogashira cross-coupling reaction opened a new avenue for the synthetic organic chemists in early 1980's for not only a new concept of developing carbon-carbon triple bond involving sp and sp3 carbons of an aryl halide and terminal alkyne but also plenty of further applications of the products in organic synthesis (Arundhathi et al., 2023; Manashi et al., 2017; Christopher et al., 2014; Fujino et al., 2016; Chinchilla& Nájera, 2007). Though, Cu was used in the beginning of this excellent reaction, later on Pd has been found to be more effective and Sonogashira cross-coupling reactions found to be an essential process in modern organic chemistry as reported in the literature (Doucet & Hierso, 2007; Beccalli et al., Alberico et al., 2007) while replacement of aryl halide with other heterocyclic halides and terminal alkyne mediated cross-couplings has been scarcely reported (Negishi & Anastasia (2003). The synthesis of new heterocycles with 5-membered oxygen-nitrogen ring has been a point of interest especially when the manufacturing and human trials of cancer vaccines (which contains mainly 5 membered O-N heterocyclic molecules and proteins) are round the corner. Environment friendly sustainable and cost-efficient organic synthesis is always advisable in today's scenario.

The present article reports the successful utilization of N-4-Bromo-phenyl-4-(Trimethylsilyl)-C-phenyl isoxazoline derivatives (Takahashi et al., 1980) as primary ingredients in Sonogashira cross-coupling reaction with phenyl acetylenes in presence of Pd and DABCO (1,4-diazabicyclo [2.2.2] octane) as catalysts and base respectively (Takahashi et al., 1980) for the synthesis of some new heterocyclic molecules with potential biological activities (Scheme 1; Table 1). Our research group has already reported many green chemistry methodologies utilizing (3+2) cycloaddition reactions and the further applications of products (isoxazolidine & isoxazolines). We found ball-milling methodology is most effective among others for its many advantages which attracts an organic chemist viz, high yield in a shorter reaction time, faster reaction rate in presence of solid phase and uses of solid sodium bicarbonate as medium during ball-milling (Chakraborty & Chettri, 2020; Ranu & Stolle, 2015; Ranu et al., 2015; Chakraborty, 2019; Chakraborty & Chhetri, 2018) 11-15. In this reported work, we have used our synthesized molecules (Takahashi et al., 1980; Chakraborty& Rai, 2018; Zhang & Li, 2010) as basic ingredients, therefore, our methodology may be also regarded as atom efficient Sonogashira cross-coupling reactions.

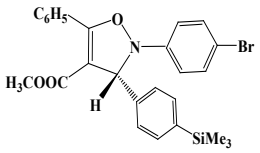
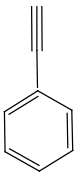
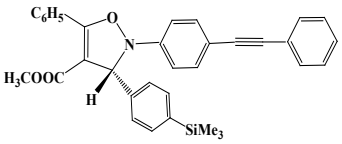
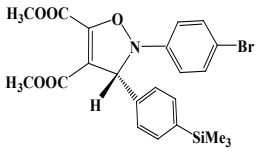
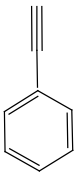
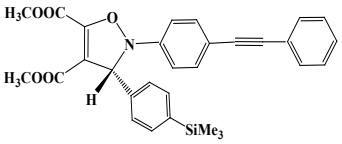
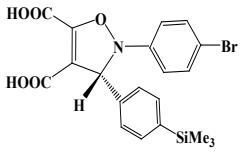
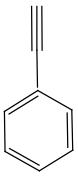
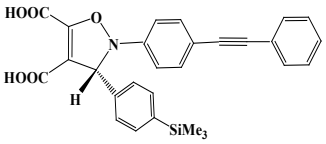
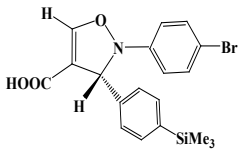
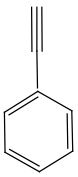
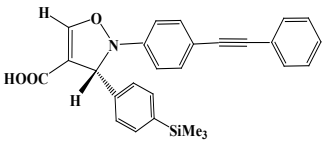
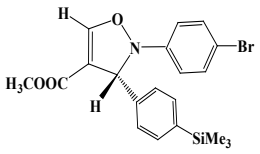
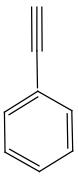
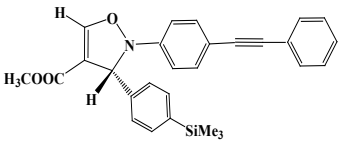
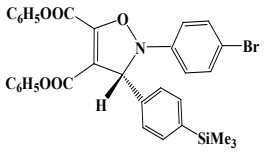
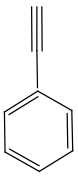
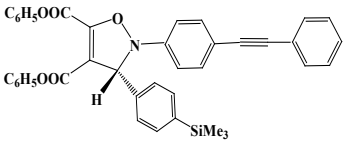


Scheme 1 - Sonogashira cross-coupling reaction for the synthesis of *N*-Biphenyl acetylene-4-(Trimethylsilyl)-*C*-phenyl isoxazoline derivatives using ball-milling technique

Results and Discussion

To execute the Sonogashira cross-coupling reaction, equimolecular amounts of N-4-Bromo-phenyl-4-(Trimethylsilyl)-C-phenyl isoxazoline derivatives along with phenyl acetylene have been ball-milled at 30-40 Hz in presence of DABCO and Pd (OAc)2 (one equivalent each) at room temperature. Solid sodium bicarbonate has been used for smooth conduction of the mechanochemical procedure. Ball-milling with solid support is always favourable as far as reaction rate and yields are concerned. Another reason could be with the addition of sodium bicarbonate, the reaction mixture became faintly alkaline, and thus the liberated HCl was neutralized. We have conducted these cross-coupling reactions with six (6) different isoxazoline derivatives having bromine atom in the N-phenyl ring (Table 1) and compared the reactions in microwave induced procedure (MWI) but we did not adopt the procedure for many reasons including work up and lower yields. We have observed that if we conduct the reactions at higher temperature (45 -600C), there is a fall in the yield. Probably, at higher temperature, the alkynes couple itself and produces by-products. Therefore, we have performed all the coupling reactions at room temperature.

Table 1 : Synthesis of new Sonogashira cross coupling products (8-13) N-4-Bromo-phenyl-4-(Trimethylsilyl)-C-phenyl-isoxazolines

Entry	Isoxazoline derivatives (2-7)	Coupling reagent[a]	Time (min)	Cross-coupling productb (8-13)	Yield[c] (%)
1	 2		4 (40)	 8	95 (82)
2	 3		4 (45)	 9	94 (80)
3	 4		5 (45)	 10	93 (76)
4	 5		5 (40)	 11	92 (76)
5	 6		5 (45)	 12	91(70)
6	 7		5 (50)	 13	90 (68)

[a]Reaction conditions: Trimethylsilyl isoxazoline (1 mmol), phenyl acetylene (1 equiv),ball-milling, DABCO, Pd (OAc)2,(20-30Hz).

[b]All products were characterized by IR,1H NMR, 13C NMR and MS spectral data.

[c]Isolated yield after purification. Figures in parentheses indicate yields obtained under MWI.

The importance of silyl nitrone in cycloadditions and the role of trimethylsilyl group in the aromatic ring was brought into the synthetic organic chemists in early 1991 by J.Y Lee et al followed by S. Saito et al in early 2000 (Sonogashira et al., 1975; Kim & Lee, 1991). Later, many significant biological activities of trimethylsilyl group have been reported and Si atom found to create a point of interest in many syntheses specially to act as antitumour agents (Ishikawa et al., 2000). The aldehyde group attached to a phenyl ring becomes more activated when trimethylsilyl group is present at the 4 position during the synthesis of trimethylsilyl nitrone. This is due to the high electron donating effect of trimethylsilyl group which enhances nitrone formation much faster than other nitrones. Si atom also plays a significant role with enhanced anti-tumor activity and reduced toxicity during anticancer study by strategically C-Si bio isosteric replacement (Kitel et al., 2021). Based on these significant activities of Si atom and trimethylsilyl group, we have chosen 4-trimethylsilyl benzaldehyde for the synthesis of N-substituted-4-trimethyl silyl nitrones and utilized in (3+2) cycloaddition reactions (Gassman et al., 1992). The solubility, permeability and stability are the crucial factors of an atom under consideration for biological study and drug efficacy. In Arundhathi et al. (2023) H NMR spectrum, trimethylsilyl group has been found to be very close or even merged with the

reference TMS in majority of the molecules at δ 0 ppm. Due to its non-interferences and chemical inertness Si and Me3Si group is very much demanding in many organic syntheses (Kitel et al., 2021).

Arundhathi et al. (2023) H NMR, Ranu et al. (2015) C NMR, IR & MS spectroscopic techniques have been used for the identification of the structures of cross-coupling products (Chakraborty et al., 2025; Pavia et al., 2024; Pauli et al., 2014). Since C-4 and C-5 protons of the isoxazoline ring are absent, therefore, stereo chemical structural pattern of the molecules are difficult to predict. C-3 protons appeared as singlet in the unfiled zone of spectrum while ester methyl and carboxylic protons appear at around 3.50 and 10.00 δ ppm respectively. Biphenyl acetylene protons have been found to be merged in all the cases with the 4-substituted phenyl protons in the spectrum. Expected signals of aromatic carbons and acetylenic carbons have been identified in Ranu et al. (2015) C NMR spectrum while molecular ion peak (M+) and base peaks (BP) have been observed in majority of the new cross-coupling products. IR absorption spectrum showed typical ester methyl and carboxylic acid group absorptions in the expected region.

Anticancer Study

In recent years, synthesis of O-N bonded five membered heterocyclic ring systems (mainly isoxazolines) and their derivatives have attracted tremendous interest among researchers as their probability to act as anticancer drugs is very high. Cytotoxicity of the Sonogashira cross-coupling compounds was determined on the basis of in vitro growth inhibition of tumour cell lines (Gandolfi & Grunanger, 1991; Srivastava et al., 2024). Different cells viz, A549 derived from human alveolar adenocarcinoma epithelial cells (ATCC No.CCL-180), HeLa derived from human cervical cancer cells (ATCC No. CCL-14), MDA-MB-167 derived from human breast adenocarcinoma cells (ATCC No. HTB-35) and MCF7 derived from human breast adenocarcinoma cells (ATCC No. HTB-40) have been used for the MTT assay. IC50 values (50% inhibitory concentration in µM) have been expressed as the average of two experiments. The effect of coupling products (8-13) on the growth of cancer cell lines have been determined using the general procedure as usually carried out at National Cancer Institute for in vitro anticancer drug study. The protein-binding dye Sulphorhodamine-B has been utilized for the estimation of cell growth (Gandolfi & Grunanger, 1991; Sanjai et al., 2024). During the period, the growth of the cells has been counted (95 cells per well in 100 mL medium) in 90 microtitre plates. The anticancer study has been conducted by keeping the cells for incubation for 30 hrs at 250C. The three different wells were setup where the cells have been kept for 30 hrs. After that, the cells have been reacted with 30% cold (5-100C) TCA followed by keeping at 200C for 1 hr. The cells have been washed and dried in air. The staining of all the cells done with Sulphorhodamine B dye and the dye was dissolved in tris-buffer solution. All the plates used in the study have been taken in shaker and kept for 10-20 minutes. The growth of the cells has been calculated utilizing optical density (OD) method. The results have been reported in terms of IC50 values (Campoccia et al., 2021). Doxorubicin was considered as standard reference.

IC50 values obtained from the six (6) Sonogashira cross-coupling products (8-13) indicates that few molecules exhibit significant cytotoxicity against human alveolar adenocarcinoma epithelial cells, human cervical cancer cells, human breast adenocarcinoma cells and human breast adenocarcinoma cells respectively. Molecules 8, 10, 11 and 13 showed comparatively more potent IC50 value against (ATCC No.CCL-180), HeLa derived from human cervical cancer cells (ATCC No. CCL-14), MDA-MB-167 derived from human breast adenocarcinoma cells (ATCC No. HTB-35) and MCF7 derived from human breast adenocarcinoma cells (ATCC No. HTB-40) as compared to other cross-coupling products. Therefore, three most potent cross-coupling products viz, 8, 10 and 13 have been chosen for cell cycle analysis and the study is going on at present.

Table 2 : IC_{50} values (µM) of new cross-coupled isoxazoline derivatives.

Compound (µg mL^{-1})	HeLa (Cervical)	MDA-MB-231 (Breast)	MCF-7 (Breast)	A549 (Lung cancer)
8	96	88	95	95
9	95	93	82	86
10	77	94	64	84
11	75	86	70	74
12	74	69	50	20
13	86	80	88	90
Doxorubicin (Standard)	0.8	2.00	0.4	0.6

Experimental

Unless otherwise stated, all reagents were obtained from commercial sources and used without further purification. Progress of all the reactions were monitored by TLC using 0.25 mm silica gel plates (Merck 60F254, UV indicator). Column chromatography was performed with silica gel (Merck- Germany) with 60–200 mesh. All other reagents and solvents were purified before starting reactions or column chromatography. Arundhathi et al. (2023) H NMR spectra were recorded on a Bruker DRX 300 (300 Hz) spectrometer at ambient temperature.(Ranu et al. (2015) C NMR spectra were recorded on a Bruker DRX 300 (75 Hz) spectrometer at ambient temperature. The coupling constants (*J*) are expressed in Hz. Infra-red spectra were recorded on a Perkin-Elmer RX 1-881 machine as a film or KBr pellets. Mass-spectrometry data was recorded using a Joel SX-102 (FAB). The ball mill used was a Retsch MM500 mixer mill digital GmbH, 42781Haan, Germany. Reactions were carried out using stainless steel jars from Retsch. Milling balls were purchased from Germany. Microwave studies were carried out in Discover Bench Mate system (Make: CEM-USA) producing continuous irradiation at 2445 MHz and infrared control system. Microwave experiments were carried out in open vessels with an effective

magnetic stirring and reflux (which avoids all problems of non-homogeneity in temperature).

General ball-milling experimental procedure for synthesis of new cross-coupling products (8-13).

N-4-Bromo-phenyl-4-(Trimethylsilyl)-C-phenyl isoxazoline derivative 8, phenyl acetylene along with 1,4-diaza-bicyclo [2.2.2] octane (DABCO) and Pd (OAc)2 [1 equivalent each] were mixed together and ball milled at 20 Hz for 20 min in a 10 mL steel vessel and 15 mm diameter balls at RT (160 C). After the completion of reaction, the crude products were extracted on a frit of thin silica layer using chloroform (3 × 10 ml). The solvent was evaporated off and the crude product was dried and re-dissolved in 1.5 ml of chloroform. The crude mixture was isolated by usual easy work-up procedure. It was directly charged on silica gel column and eluted with a mixture of ethyl acetate: n-hexane (1:8) resulting pure cross-coupling product 8 (95%; Entry 1, Table 1, Scheme 1). Same methodology was adopted for the synthesis of other cross-coupling products (9 to 13).

General microwave induced experimental procedure for synthesis of new cross-coupling products (8-13).

N-4-Bromo-phenyl-4-(Trimethylsilyl)-C-phenyl isoxazoline derivative 8, phenyl acetylene along with 1,4-diaza-bicyclo [2.2.2] octane (DABCO) and Pd (OAc)2 [1 equivalent each] were mixed together and taken in a 25 ml Erlenmeyer flask. EtOAc (3-4 ml) was added to the flask. A paste of the added ingredients was made and it was subjected to microwave irradiation at medium power (50%) for 40 minutes. The completion of reaction was monitored by TLC. The reaction mixture was cooled to RT and extracted with diethyl ether. The product was concentrated in a rotary vacuum evaporator and finally purified by recrystallization from ethanol to afford pure fluoro-isoxazolidine 8 (82%; Table 1). Same methodology was adopted for the synthesis of other cross-coupling products (3-13).

The experimental results furnished below are conducted in both the procedures and the yields were compared in Table 1.

***(S)*-2-diphenylethyne-3-(4-trimethylsilyl)-2,3-dihydroisoxazole-5-phenyl-4-carboxylic acid**

Yellowish white crystals. M.P: 1360C. Yield 95%; R_f = 0.66; IR (KBr): υmax 3090 (m), 3005 (m), 1760 (s), 1680 (s), 1620 (m), 1590 (m), 1450 (m), 805 (s), 776 (s) cm^{-1}; 1H NMR ($CDCl_3$):δ 7.77-7.00 (m, 10H & 8H & phenyl protons), 3.57 (s, 3H, ester methyl protons), 1.00 (s, 1H, C_3H); 13C NMR ($CDCl_3$): δ 172.50 (carbonyl carbon), 138.5, 138.0, 137.5, 137. 0, 136.5, 136.0, 134.5, 134.0, 133.5, 132.5, 132.0 (phenyl carbons), 88.5 (C5), 75.5 (C3), 56.5 (C4), 28.5 (acetylenic carbons); FAB-MS (m/z): 569, (M+, 100%), 392, 239 (BP), 177, 145, 77, 67; Anal. Calcd. for C40H31ONSi: C, 84.35; H, 5.44; N, 2.46%. Found: C, 83.50; H, 5.36; N, 2.10.

***(S)*-dimethyl-2-diphenylethyne-3-(4-trimethylsilyl)-2,3-dihydroisoxazole-4,5-dicarboxylate**

Red liquid. Yield 90%; Rf= 0.60; IR (KBr): υ_{max}3290 (m), 2180 (m), 1740 (s), 1670 (s), 1620 (s), 1260 (s), 870 (m), 776 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$):δ 7.70-7.10 (m, 8H & 5H phenyl protons), 3.61 (s, 6H, 2-ester methyl protons), 1.00 (s, 1H, C_3H); ^{13}C NMR ($CDCl_3$): δ 172.50, 170.0 (carbonyl carbons), 138.0, 137.5, 137.0, 136.5, 135.0, 134.5, 134.0, 133.5, 131.5, 131.0 (phenyl carbons), 87.0 (C_5), 77.5 (C_4), 55.5 (C_3), 30.0, 29.5 (acetylenic carbons); FAB-MS (m/z): 447, (M+, 100%), 298, 270, 177, 145, 121 (BP), 77; Anal. Calcd. for C30H29ONSi: C, 80.53; H, 6.48; N, 3.13%. Found: C, 80.45; H, 6.30; N, 2.95.

***(S)*-2-diphenylethyne-3-(4-trimethylsilyl)-2,3-dihydroisoxazole-4,5-dicarboxylic acid**

Colourless thick liquid. Yield 90%; Rf= 0.64; IR (KBr): υ_{max}3180 (m), 2990 (br), 1760 (s), 1485 (s), 1360 (s), 1210 (s), 790 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 10.00 (s, 2H, 2xCOOH), 7.70-7.20 (m, 8H & 5H phenyl protons), 3.40 (s, 1H, C_3H); ^{13}C NMR ($CDCl_3$): δ 170.5, 169.0 (carbonyl carbons), 137.0, 136.5, 136.0, 135.5, 135.0, 134.5, 134.0, 131.5, 131.5, 130.0 (phenyl carbons), 89.0 (C_5), 76.5 (C_4), 57.0 (C_3), 28.0, 27.0 (acetylenic carbons); FAB-MS (m/z): 419, (M+, 100%), 242, 298, 270, 177, 145, 97 (BP), 77; Anal. Calcd. for $C_2$8$H_2$5ONSi: C, 80.19; H, 5.96; N, 3.34%. Found: C, 80.10; H, 5.80; N, 3.24.

***(S)*-2-diphenylethyne-3-(4-trimethylsilyl)-2,3-dihydroisoxazole-4-carboxylic acid**

Red thick liquid. Yield 88%; Rf = 0.66; IR (KBr): υ_{max}3230 (m), 2240 (m), 1740 (s), 1715 (s), 1680 (s), 1320 (s), 780 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 10.00 (s, ^{1}H, COOH), 7.74-7.30 (m, 8H & 5H phenyl protons), 3.40 (s, ^{1}H, C5H), 1.00 (s, 1H, C_3H); ^{13}C NMR ($CDCl_3$): δ 169.0 (carbonyl carbon), 136.5, 136.0, 135.5, 135.0, 134.5, 134.0, 133.5, 132.0, 131.0, 130.0 (phenyl carbons), 87.0 (C_5), 76.0 (C_4), 32.0 (C_3), 28.0, 27.0 (acetylenic carbons); FAB-MS (m/z): 407, (M+, 100%), 262, 230, 177, 145, 85 (BP), 77; Anal. Calcd. for $C_2$7$H_2$5ONSi: C, 79.60; H, 6.14; N, 3.43%. Found: C, 79.16; H, 6.00; N, 3.14.

***(S)*-2-diphenylethyne-3-(4-trimethylsilyl)-2,3-dihydroisoxazole-4-carboxylate**

Red thick liquid. Yield 88%; Rf = 0.66; IR (KBr): υ_{max}3230 (m), 2240 (m), 1740 (s), 1715 (s), 1680 (s), 1320 (s), 780 (s) cm^{-1}; 1H NMR ($CDCl_3$): δ 7.77-7.20 (m, 8H & 5H phenyl protons), 3.57 (s, 3H, $COOCH_3$), 3.40 (s, 1H, C5H), 2.90 (s,1H, C_5H), 1.00 (s, 1H, C_3H); 13C NMR ($CDCl_3$): δ 170.0 (carbonyl carbon), 136.0, 135.0, 134.5, 134.0, 133.0, 132.5, 132.0, 131.0, 130.5, 130.0 (phenyl carbons), 86.0 (C_5), 77.0 (C_4), 45.0 (C_3), 28.5, 27.0 (acetylenic carbons); FAB-MS (m/z): 421, (M+, 100%), 276, 244, 230, 177, 145, 99 (BP), 77; Anal. Calcd.for $C_{28}H_{27}$ONSi: C, 79.80; H, 6.41; N, 3.32%. Found: C, 79.20; H, 6.25; N, 3.10.

***(S)*-diphenyl-2-diphenylethyne-3-(4-trimethylsilyl)-2,3-dihydroisoxazole-4,5-dicarboxylate**

Red liquid. Yield 90%; Rf= 0.60; IR (KBr): υ_{max}3290 (m), 2180 (m), 1740 (s), 1670 (s), 1620 (s), 1260 (s), 870 (m), 776 (s) cm^{-1}; ^{1}H NMR (CDCl3): δ 7.70-7.25 (m, 10H, 8H, & 5H

phenyl protons), 1.00 (s, 1H, C_3H); ^{13}C NMR ($CDCl_3$): δ 171.0, 169.0 (carbonyl carbons), 138.0,137.5, 137.0, 136.5, 136.0, 135.0, 134.5, 134.0, 133.0, 132.5, 132.0, 131.0, 130.5, 130.0 (phenyl carbons), 86.5 (C5), 76.0 (C4), 44.0 (C3), 28.5, 27.0 (acetylenic carbons); FAB-MS (m/z): 571, (M+, 100%), 426, 394, 249 (BP), 177, 145, 77; Anal. Calcd.for $C_{40}H_{33}ONSi$: C, 84.06; H, 5.77; N, 2.45%. Found: C, 83.60; H, 5.50; N, 2.28%.

Conclusion

In summary, Sonogashira cross-coupled molecules were synthesized from isoxazoline derivatives as basic ingredients for the reaction along with phenyl acetylene in ball-mill procedure and solvent-free conditions. This protocol is very promising and therefore, it should attract the attention of organic chemists working in the field of synthetic organic chemistry. This methodology also opens a new pavement for a new aspect of cross-coupling reaction. Moreover, this methodology is very simple, cost efficient and is safe for the mankind as well as for the environment. Few synthesized new molecules have been found to possess potential anticancer activities against few human cells and therefore creating an opportunity to have further studies on cell-cycle analysis for these kind of molecules so as to see their potential as broad-spectrum anticancer compounds.

Conflicts of Interest

There are no conflicts to declare.

Data Statement

All data are available in the manuscript and further informations can be obtained from the corresponding author upon request.

Acknowledgements

The authors are grateful to SAIF, CDRI (Central Drug Research Institute), Lucknow, India for providing IH NMR, 13C NMR, IR & FAB-MS spectroscopic data (2020). BC is also grateful to School of Chemistry, Cardiff University, Wales, UK for providing facilities to learn mechanochemical procedures and Department of Biotechnology, New Delhi, Government of India for providing *Overseas Associateship-Fellowship in 2019*.

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