Synthesis of substituted-3-iodo-1*H*-pyrazole derivatives and their further modification under Sonogashira cross-coupling reaction conditions

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Abstract

A convenient synthetic route for preparation of valuable synthetic intermediates - 1-(1-ethoxyethyl)-3-iodo-1*H*-pyrazole derivatives has been developed. During this work protection reaction of N-H bond in substituted 3-iodo-1*H*-pyrazole derivatives with ethyl vinyl ether and migration of ethoxyethyl protecting group was investigated. Synthetic possibilities of Sonogashira cross-coupling reactions of substituted 1-(1-ethoxyethyl)-3-iodo-1*H*-pyrazole derivatives with phenylacetylene were studied and evaluated.

Keywords: Sonogashira cross-coupling, 1-(1-ethoxyethyl)-3-iodo-1*H*-pyrazole, ethoxyethyl protecting group migration

Introduction

Pyrazole scaffolds can be found in a number of small molecules possessing biological activity.[1,2] Also it is used in design of new OLED materials.[3] Substituted pyrazole derivatives may be used as ligands for transition metal-catalyzed reactions.[4] Moreover, they are very useful synthetic intermediates for other heterocyclic systems such as substituted bis(pyrazolo[4,3-*d*][1,2]diazepinones,[5] substituted octahydro-1*H*-benzo[*g*]indazole derivatives,[6] substituted 1*H*-pyrazolo[3,4-*c*]pyridines[7] and other.

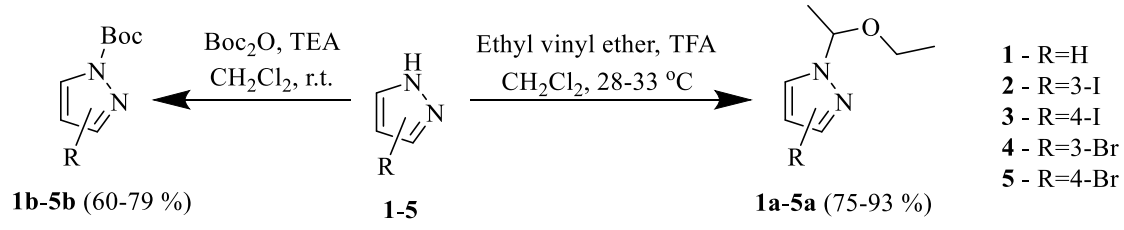
Electrophilic substitution in the pyrazole ring usually occurs in the 4-th position. Thus, one of the most common ways for the synthesis of 3-substituted pyrazole derivatives is based on the formation of pyrazole ring via condensation of functionalized 1,3-dicarbonyl compounds with hydrazines.[8] Such methods usually generate mixture of regioisomers and cause problems with isolation of products. In addition, only limited selection of dicarbonyl compounds are readily available. Another pathway for the synthesis of pyrazole derivatives with substituents in 3,4-, 4,5- or 3,5-th positions involves palladium catalyzed cross-coupling reactions.[9-11] Despite the fact that

number of reports on successful application of cross-coupling in pyrazole chemistry increases, this field is not yet fully investigated.

2-Nitro- and 2-formylhetarylacetylenes are valuable intermediates of new heterosystems.[12-15] Previous studies of intramolecular cyclisation or cycloisomerisation of 2-formylhetarylacetylenes has showed that the structure of products can vary depending on the nature of used materials.[12,16] For further studies of cyclisation reactions 1-(1-ethoxyethyl)-3-(phenylethynyl)-1*H*-pyrazole-4-carbaldehyde and 1-(1-ethoxyethyl)-3-nitro-4-(phenylethynyl)-1*H*-pyrazole were synthesized. Herewith the Sonogashira cross-coupling reaction of 1-(1-protected)-3-iodo-1*H*-pyrazole derivatives with phenylacethylene was investigated and applied for the synthesis of N-unprotected pyrazoles.

Results and discussion

As pyrazoles themselves are known as ligands for transition metals,[4] protection of N-H group of 3-iodo-1*H*-pyrazole derivatives were necessary in our investigations of cross-coupling reactions. 1*H*-Pyrazoles **1-5** were protected using Boc anhydride and ethyl vinyl ether. N-ethoxyethyl (EtOEt) and N-Boc protected pyrazole derivatives (**1a-5a** and **1b-** 5**b**, respectively) were synthesized in good to excellent yields (Scheme 1) and used in reactions with lithium organic compounds and Sonogashira cross-coupling reactions. Unfortunately, Boc protecting group was not stable enough both in reactions with lithium organic compounds and during GC-MS analysis. Thus we have decided to focus our further experiments on EtOEt protected pyrazole derivatives.

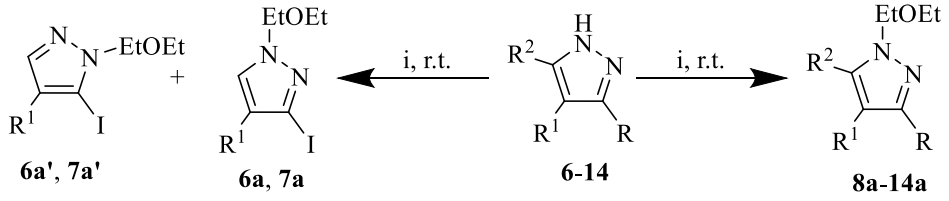


Scheme 1. Protection of free N-H group in 1*H*-pyrazole derivatives **1-5**.

According to literature reports, EtOEt protecting group can be easily introduced and removed from pyrazole ring in mild acidic conditions.[17-19] Tetrahydropyran (THP) group is recommended for the synthesis of unsymmetrical pyrazole derivatives.[20] Usually protection reaction of pyrazole ring with EtOEt or THP groups are performed by heating reaction mixture of starting pyrazoles with ethyl vinyl ether or dihydropyran and catalytic amount acid 40-50 °C. Deprotection in acidic conditions is reversible and the removal of ethyl vinyl ether or 3,4-dihydro-2*H*-pyran is necessary to complete this reaction. Due to lower boiling temperature ethyl vinyl ether appeared to be preferable.

We found that the exothermic effect of addition of ethyl vinyl ether to N-H bond in syntheses of larger scale is quite significant. In higher temperatures reaction tends to accelerate and can get out of control. The control reaction can be achieved by portionwise addition of ethyl vinyl ether to the reaction mixture at 28 – 33 ºC in dichloromethane, with catalytic amount of trifluoroacetic acid (TFA).

The monitoring of reaction of 3,4-diiodo-1*H*-pyrazole (**6**) and 4-bromo-3-iodo-1*H*-pyrazole (**7**) with ethyl vinyl ether indicated the migration of EtOEt protecting group in acidic conditions. After keeping reaction mixture at room temperature for 2 h, in both cases the mixtures of isomers were detected. According GC-MS analysis, the ratios **6a** to **6a'** and **7a** to **7a'** were 1:1 (Scheme 2, table 1). After keeping the reaction mixtures at room temperature for prolonged period of time (20 – 78 hours) only traces of 5-iodo isomers **6a'** and **7a'** were left. 4-Bromo(iodo)-1-(1-ethoxyethyl)-3-iodo-1*H*-pyrazoles **6a** and **7a** were isolated in excellent yields. Di-substituted EtOEt-protected pyrazole derivatives **8a** – **14a** were synthesized applying the same method in good yields (Scheme2, Table 1).



r.t. 2h:	50 %	50 %
r.t. 20h:	20 %	80 %
r.t. 78h:	3 %	97 %

6: R^1=I; **7**: R^1=Br;
8: R=I, R^1=H, R^2=CF_3; **9**: R=I,R^1=NO_2; R^2=H;
10: R=NO_2, R^1=I, R^2=H; **11**: R=I, R^1=COOEt, R^2=H;
12: R=I, R^1=Me, R^2=H; **13**: R=Br, R^1=NO_2, R^2=H;
14: R=Br, R^1=COOEt, R^2=H;

Scheme 2. Protection of N-H group in disubstituted 1*H*-pyrazole derivatives **6-14**. i: ethyl vinyl ether, TFA, CH_2Cl_2, 28-33 °C, then room temperature.

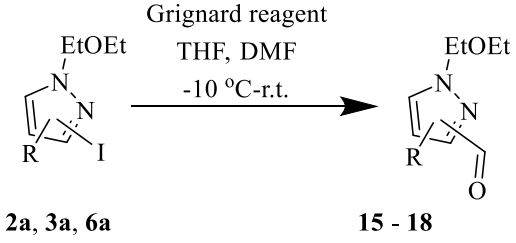
It is known that 1-(1-ethoxyethyl)-4-iodo-1*H*-pyrazole (**3a**) can be easily converted to Grignard reagents using alkyl magnesium bromides.[17] 1-(1-Ethoxyethyl)-1*H*-pyrazole-4-carbaldehyde (**16**) was synthesized in good yield using this intermediate. Thus, we wanted to compare the reactivity of 1-(1-ethoxyethyl)-3-iodo-1*H*-pyrazole (**2a**), 4-iodopyrazole **3a** and 3,4-diiodopyrazole **6a** towards alkyl magnesium halides and to evaluate the possibilities of application of Grignard reagents in derivatization of iodopyrazoles to pyrazole aldehydes. It is known that quantity of final pyrazole aldehydes reflects with the quantity of metalated pyrazoles, because usually these reactions occurs instantaneously. Unfortunately, 3-iodo derivative **2a** didn't react with ethylmagnesium bromide. Only 25 % conversion of **2a** to aldehyde **15** was achieved using 2-propylmagnesium bromide - lithium bromide (Scheme 3, table 2). Thus, we were expecting that EtMgBr could selectively react with iodo atom in 4-th position of 3,4-diiodo derivative **6a**. Full conversion of **6a** was achieved

within 30 minutes at +5 °C, however the formation of both available isomers - 1-(1-ethoxyethyl)-4-iodo-1*H*-pyrazole-3-carbaldehyde (**17**) and 1-(1-ethoxyethyl)-3-iodo-1*H*-pyrazole-4-carbaldehyde (**18**) in ratio 1:1 was observed. Decreasing reaction temperature increases selectivity of substitution (at -10 °C ratio of **17** to **18** is 1 to 2, at -40 °C ratio reaches 1 to 4). However the starting compound is not fully consumed, by performing iodo-EtMgBr exchange reaction at -10 °C degrees after 2 hours - 10 % of **6a** was left unreacted, at -40 °C – 30 %. Analogous bromopyrazoles **4a** and **5a** did not react with alkyl magnesium halides.

Table 1. Synthesis of N-ethoxyethyl protected pyrazoles **6a**-**14a**

Starting material				Time, h	Product Nr.	Yield, %*
Nr	R	R^1	R^2			
6	I	I	H	78	**6a**	86
7	I	Br	H	78	**7a**	77
8	I	H	CF_3	14	**8a**	75
9	I	NO_2	H	14	**9a**	77
10	NO_2	I	H	14	**10a**	80
11	I	COOEt	H	14	**11a**	43
12	I	Me	H	78	**12a**	80
13	Br	NO_2	H	24	**13a**	75
14	Br	COOEt	H	24	**14a**	83

*Isolated yield.



2a, **3a**, **6a** **15 - 18**

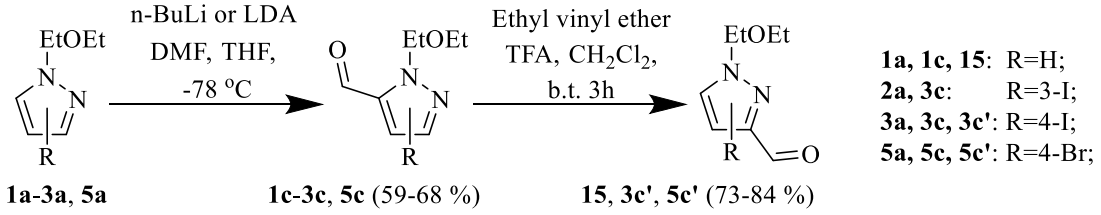
Scheme 3. Reaction of 1-(1-ethoxyethyl)-3-iodo-, 4-iodo- and 3,4-diiodo-1*H*-pyrazole derivatives **2a**, **3a**, **6a** with Grignard reagents.

There are some suggestions for the synthesis of pyrazole derivatives in high yields via halogen-lithium exchange reaction.[21,22] Usually such reactions are performed by direct lithiation at 5-th position or by halogen-lithium exchange reaction of halogen atom at 4-th or 5-th positions of the pyrazole ring. Our experiment has shown, that N-EtOEt group acts as ortho-directing group. Thus, direct ortho lithiation reaction of N-EtOEt protected pyrazole derivatives was performed using n-BuLi (**1a**) or lithium diisopropylamide (LDA) (**2a**, **3a**, **5a**) as lithiating agents and pyrazole aldehydes **1c** – **3c**, **5c** were synthesized in good yields (Scheme 4).

Table 2. Synthesis of N-EtOEt pyrazole aldehydes **15**, **16**, **17** and **18**

Starting material	R	I	Grignard reagents	Product	Substituents	Conversion* (Yield **)
2a	4-H	3-I	EtMgBr	**15**	4-H; 3-CHO	0 %
			2-PrMgBr/LiBr			25 % (19 %)
3a	3-H	4-I	EtMgBr	**16**	3-H; 4-CHO	85 % (72 %)
6a	3-I	4-I	EtMgBr	**17**	4-I; 3-CHO	30 % (10 %)
				18	3-I; 4-CHO	65 % (55 %)

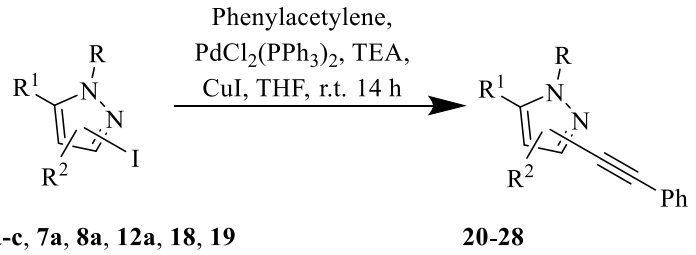
* GC-MS data;**Isolated yield.



Scheme 4. Reactions of 1-(1-ethoxyethyl)-1*H*-pyrazole derivatives **1a**-**3a**, **5a** with lithium organic compounds

Ethoxyethyl protecting group in compounds **1c**-**3c**, **5c** appeared to be very sensitive to acidic conditions. The migration of protecting group can be performed by heating 1-(1-ethoxyethyl)-1*H*-pyrazole-5-carbaldehyde (**1c**), 1-(1-ethoxyethyl)-4-iodo-1*H*-pyrazole-5-carbaldehyde (**3c**) or 4-bromo-1-(1-ethoxyethyl)-1*H*-pyrazole-5-carbaldehyde (**5c**) in dichloromethane at 40 °C for 3 h, using catalytic amount of trifluoroacetic acid and 5% of ethyl vinyl ether for prevention of deprotection. Thus, 1-(1-ethoxyethyl)-1*H*-pyrazole-3-carbaldehyde (**15**), 1-(1-ethoxyethyl)-4-iodo-1*H*-pyrazole-3-carbaldehyde (**3c'**) and 4-bromo-1-(1-ethoxyethyl)-1*H*-pyrazole-3-carbaldehyde (**5c'**) were synthesized in good yields. Structure of final products was proven by ^{1}H-NMR, but significantly differs only chemical shift of protecting group NCH proton. Also we have noticed that the acidity of silica gel, which was used for purification, was enough for the migration of protecting group via elimination/addition of ethyl vinyl ether. However, migration could be prevented by washing silica gel column with 5% triethylamine (TEA) solution in dichloromethane before chromatography. Thus, ethoxyethyl protecting group can be recommended as switchable protecting group for synthesis of pyrazole derivatives as well as tetrahydropyran group.[20]

Reactions of substituted 1-(1-protected)-3-iodo-1*H*-pyrazole derivatives **2a-c**, **7a**, **8a**, **12a**, **18** and **19** with phenyl acetylene were successfully performed under standard Sonogashira cross-coupling conditions (Scheme 5). Compounds **20**-**27** were synthesized in high yields (Table 3).



2a-c, **7a**, **8a**, **12a**, **18**, **19** **20-28**

Scheme 5. Sonogashira cross-coupling reaction of substituted iodopyrazole derivatives.

Table 3. Synthesis of compounds **20**-**30** via Sonogashira cross-coupling reaction.

Starting material					Product	Yield,
Nr	R	R^1	R^2	I	Nr.	%*
2b	Boc	H	4-H	3-I	**20**	65
2a	EtOEt	H	4-H	3-I	**21**	63
2c	EtOEt	CHO	4-H	3-I	**22**	80
7a	EtOEt	H	4-Br	3-I	**23**	64
8a	EtOEt	CF_3	4-H	3-I	**24**	73
12a	EtOEt	H	4-Me	3-I	**25**	70
18	EtOEt	H	4-CHO	3-I	**26**	87
19	Me	H	4-H	3-I	**27**	82
9a	EtOEt	H	4-NO_2	3-I	-	0
11a	EtOEt	H	4-COOEt	3-I	-	0
10a	EtOEt	H	4-I	3-NO_2	**28**	58

*Isolated yield

Analogous bromopyrazoles **4a** and **5a** didn't react with phenyl acetylene under various Sonogashira cross-coupling conditions. Unfortunately 3-iodo-pyrazole derivatives **9a** with nitro group and **11a** with ethoxycarbonyl substituents at 4-th-pyrazole ring position were also unreactive under various conditions, only starting compounds **9a** and **11a** were obtained during GC-MS analysis. To the contrary to compound **9a**, it's isomer 1-(1-ethoxyethyl)-4-iodo-3-nitro-1*H*-pyrazole (**10a**) has formed cross-coupling product **28** in 58 % yield.

Experimental Section

General. Melting points were determined in open capillaries and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz respectively on a Brucker 400 instrument with $CDCl_3$ or DMSO-d_6 solvents using residual solvent peaks as internal standards. Mass spectra were recorded on a Shimadzu QP2010 instrument equipped Restec Rtx-1701 w/Integra-Guard column

(30 m, 0.25 mm ID, 0.25 μm thickness). HRMS spectra were obtained on a mass spectrometer Dual-ESI Q-TOF 6520 (Agilent Technologies). Silica gel 60 F254 aluminum plates (Merck) were used for TLC analysis. Column chromatography was performed on silica gel 60 (0.04 – 0.063 mm) (Roth).

General synthetic procedure for the synthesis of N-Boc protected pyrazole derivatives 1b-5b. To a solution of pyrazole **1-5** (1 equiv.) and triethylamine (1.5 equiv.) in dichloromethane (for 0.05 mol of pyrazole – 50 mL of dichloromethane were user) Di-tert-butyl dicarbonate (1.2 equiv) were added at room temperature and left to stir overnight. Dichloromethane was washed with saturated $NaHCO_3$ solution (1×25 mL – for 50 mL of dichloromethane) then with deionized H_2O (1 × 25 mL). Organic layer was dried with anhydrous Na_2SO_4, and evaporated under reduced pressure.

***tert*-Butyl 1*H*-pyrazole-1-carboxylate (1b)**. Reaction was performed in 0.069 mol scale of 1*H*-pyrazole (**1**). Purification by distillation gave the titled compound as slightly yellow oil, yield 59%, 6.8 g, bp 48 °C at 1.5 mbar (bp 130 °C at 2 mmHg).[23] ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.58 (s, 9H, 3×CH_3), 6.53 (dd, *J* 2.8, 1.6 Hz, 1H, Ar-H), 7.80 (d, *J* 0.9 Hz, 1H, Ar-H), 8.26 (d, *J* 3.6 Hz, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 27.9, 85.2, 109.5, 131.7, 144.4, 147.6. MS, *m/z* (%) 168 (4), 109 (19), 95 (7), 57 (100).

***tert*-Butyl 3-iodo-1*H*-pyrazole-1-carboxylate (2b).** Reaction was performed in 0.052 mol scale of 3-iodo-1*H*-pyrazole (**2**). Purification by recrystallization from n-hexane gave the titled compound as white crystals, yield 78.5%, 12 g, mp 82-84°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.57 (s, 9H, 3×CH_3), 6.76 (d, *J* 2.8 Hz, 1H, Ar-H), 8.16 (d, *J* 2.8 Hz, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 27.9, 86.1, 104.6, 118.2, 133.6, 146.4. MS, *m/z* (%) 194 (M-Boc, 100), 167 (25), 128 (2), 40 (36). HRMS (ES) calculated for $[M+Na]^+$ $C_8H_{11}IN_2NaO_2$: 316.9757; found 316.9757.

***tert*-Butyl 4-iodo-1*H*-pyrazole-1-carboxylate (3b).** Reaction was performed in 0.052 mol scale of 4-iodo-1*H*-pyrazole (**3**). Purification by recrystallization from n-hexane gave the titled compound as white crystals, yield 78.5%, 12 g, mp 72-74 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.57 (s, 9H, 3×CH_3), 7.89 (d, *J* 0.6 Hz, 1H, Ar-H), 8.46 (d, *J* 0.6 Hz, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 27.9, 63.8, 86.0, 135.9, 146.4, 148.8. MS, *m/z* (%) 194 (M-Boc, 100), 167 (2), 128 (2), 67 (17), 40 (24). HRMS (ES) calculated for $[M+Na]^+$ $C_8H_{11}IN_2NaO_2$: 316.9757; found 316.9757.

***tert*-Butyl 3-bromo-1*H*-pyrazole-1-carboxylate (4b).** Reaction was performed in 0.136 mol scale of 3-bromo-1*H*-pyrazole (**4**). Purification by recrystallization from n-hexane gave the titled compound as white crystals, yield 80.4%, 27 g, mp 33-35 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.58 (s, 9H, 3×CH_3), 6.72 (d, *J* 2.8 Hz, 1H, Ar-H), 8.30 (t, *J* 2.8 Hz, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 27.8, 86.3, 112.6, 131.8, 134.1, 146.4. MS, *m/z* (%) 148 : 146 (M-Boc : M-Boc, 100 : 100), 121 (21), 119 (21), 67 (9), 40 (51). HRMS (ES) calculated for $[M+Na]^+$ $C_8H_{11}BrN_2NaO_2$: 268.9896; found 268.9896.

***tert*-Butyl 4-bromo-1*H*-pyrazole-1-carboxylate (5b).** Reaction was performed in 0.068 mol scale of 4-bromo-1*H*-pyrazole (**5**). Purification by recrystallization from n-hexane gave the titled compound as white crystals, yield 79.6%, 13.4 g, mp. 43-45 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.57 (s, 9H, 3×CH_3), 7.94 (d, *J* 0.6 Hz, 1H, Ar-H), 8.54 (d, *J* 0.6 Hz, 1H, Ar-H). ^{13}C NMR (100

MHz, DMSO-d_6) δ 27.8, 86.1, 97.2, 131.7, 144.7, 146.5. MS, *m/z* (%) 148 : 146 (M-Boc : M-Boc, 100 : 100), 121 (21), 119 (21), 94 (13), 92 (13), 67 (12), 40 (33). HRMS (ES) calculated for $[M+Na]^+$ $C_8H_{11}BrN_2NaO_2$: 268.9896; found 268.9896.

General synthetic procedure for the synthesis of N-EtOEt protected pyrazole derivatives 1a-13a.

To a solution of pyrazole **1-13** (1 equiv.) and trifluoroacetic acid (0.01 equiv.) in dichloromethane (for 1 mol of pyrazole - 1 L of dichloromethane were used) ethyl vinyl ether (1.27 equiv.) was added dropwise, keeping the temperature between 28-32 ºC (exothermic reaction) and left to stir at room temperature for 12-78 hours. Dichloromethane was washed with saturated $NaHCO_3$ solution (1 × 250 mL – for 1 L of dichloromethane) then with deionized H_2O (1 × 250 mL). Organic layer was dried with anhydrous Na_2SO_4, and evaporated under reduced pressure. Products were purified by distillation or recrystallization.

1-(1-Ethoxyethyl)-1*H*-pyrazole (1a). Reaction was performed in 20.48 mol scale of 1*H*-pyrazole (**1**). Purification by distillation gave the titled compound as slightly yellow oil, yield 93%, 2686 g, bp 52 ºC at 9 mbar. (bp 71-74°C at 20 mmHg).[24] ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.02 (t, *J* 7.0 Hz, 3H, CH_2CH_3), 1.58 (d, *J* 6.0 Hz, 3H, $CHCH_3$), 3.14 (dq, *J* 9.6, 7.1 Hz, 1H, $CHHCH_3$), 3.44 – 3.36 (m, 1H, $CHHCH_3$), 5.55 (q, *J* 6.0 Hz, 1H, NCH), 7.89 (t, *J* 2.0 Hz, 1H, Ar-H), 7.49 (d, *J* 1.3 Hz, 1H, Ar-H), 7.89 (d, *J* 2.0 Hz, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 15.2, 21.7, 63.3, 86.4, 106.2, 128.3, 139.1. MS, *m/z* (%) 140 (1), 125 (2), 96 (49), 73 (12), 45 (100).

3-Iodo-1-(1-ethoxyethyl)-1*H*-pyrazole (2a). Reaction was performed in 0.26 mol scale of 3-jodo-1*H*-pyrazole (**2**). Purification by distillation gave the titled compound as slightly yellow oil, yield 92%, 70 g, bp 72 ºC (1.8 mbar). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.03 (t, *J* 7.0 Hz, 3H, CH_2CH_3), 1.56 (d, *J* 6.0 Hz, 3H, $CHCH_3$), 3.17 (tt, *J* 9.6, 5.4 Hz, 1H, $CHHCH_3$), 3.45 – 3.36 (m, 1H, $CHHCH_3$), 5.54 (q, *J* 6.0 Hz, 1H, NCH), 6.53 (d, *J* 2.4 Hz, 1H, Ar-H), 7.84 (d, *J* 2.4 Hz, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 15.2, 21.6, 63.6, 86.9, 96.3, 114.9, 131.2. MS, *m/z* (%) 266 (7), 222 (41), 207 (14), 193 (11), 95 (26), 73 (56), 45 (100). HRMS (ES) calculated for $[M+Na]^+$ $C_7H_{11}IN_2NaO$: 288.9808; found 288.9809.

4-Iodo-1-(1-ethoxyethyl)-1*H*-pyrazole (3a). Reaction was performed in 9.43 mol scale of 4-iodo-1*H*-pyrazole (**3**). Purification by distillation gave the titled compound as white oil, yield 93%, 2327 g, bp 70 ºC (2.2 mbar). Lit.[19] bp 74-76°C (0.5 torr). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.03 (t, *J* 7.0 Hz, 3H, CH_2CH_3), 1.57 (d, *J* 6.0 Hz, 3H, $CHCH_3$), 3.17 (dq, *J* 9.6, 7.0 Hz, 1H, $CHHCH_3$), 3.40 (dq, *J* 9.6, 7.0 Hz, 1H, $CHHCH_3$), 5.54 (q, *J* 6.0 Hz, 1H, NCH), 7.58 (s, 1H, Ar-H), 8.13 (s, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 15.1, 21.5, 58.5, 63.6, 87.0, 133.0, 144.0. MS, *m/z* (%) 266 (31), 222 (42), 194 (48), 72 (91), 45 (100). HRMS (ES) calculated for $[M+Na]^+$ $C_7H_{11}IN_2NaO$: 288.9808; found 288.9809.

3-Bromo-1-(1-ethoxyethyl)-1*H*-pyrazole (4a). Reaction was performed in 0.136 mol scale of 3-bromo-1*H*-pyrazole (**4**). Purification by distillation gave the titled compound as white oil, yield 85.6%, 25.5 g, bp 68 ºC at 3.6 mbar. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.04 (t, *J* 7.0 Hz, 3H, CH_2CH_3), 1.57 (d, *J* 6.0 Hz, 3H, $CHCH_3$), 3.19 (dq, *J* 9.6, 7.0 Hz, 1H, $CHHCH_3$), 3.38-3.46 (m,

1H, $CHHCH_3$), 5.52 (q, *J* 6.0 Hz, 1H, NCH), 6.45 (d, *J* 2.4 Hz, 1H, Ar-H), 7.95 (d, *J* 2.4 Hz, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 15.1, 21.5, 63.6, 87.1, 108.8, 125.3, 131.6. MS, *m/z* (%) 220 : 218 (2 : 2), 176 (16), 174 (16), 161 (10), 159 (10), 148 (9), 146 (9), 94 (12), 73 (96), 45 (100). HRMS (ES) calculated for $[M+Na]^+$ $C_7H_{11}BrN_2NaO$: 240.9947; found 240.9946.

4-Bromo-1-(1-ethoxyethyl)-1*H*-pyrazole (5a). Reaction was performed in 0.136 mol scale of 3-bromo-1*H*-pyrazole (**5**). Purification by distillation gave the titled compound as white oil, yield 73.3%, 21.8 g, bp 55 ºC at 2.6 mbar. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.03 (t, *J* 7.0 Hz, 3H, CH_2CH_3), 1.57 (d, *J* 6.0 Hz, 3H, $CHCH_3$), 3.19 (dq, *J* 9.6, 7.0 Hz, 1H, $CHHCH_3$), 3.41 (dq, *J* 9.6, 7.0 Hz, 1H, $CHHCH_3$), 5.52 (q, *J* 6.0 Hz, 1H, NCH), 7.60 (s, 1H, Ar-H), 8.18 (s, 1H, Ar-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 15.1, 21.5, 63.6, 87.4, 93.1, 128.8, 139.5. MS, *m/z* (%) 220 : 218 (5 : 5), 176 (16), 174 (16), 148 (12), 146 (12), 94 (13), 73 (74), 45 (100). HRMS (ES) calculated for $[M+Na]^+$ $C_7H_{11}BrN_2NaO$: 240.9947; found 240.9946.

1-(1-Ethoxyethyl)-3,4-diiodo-1*H*-pyrazole (6a). Reaction was performed in 0.047 mol scale of 3,4-diiodo-1*H*-pyrazole (**6**). Purification by recrystallization from n-hexane gave the titled compound as slightly yellow crystals, yield 85.9%, 15.8 g, mp 55-57 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.04 (t, *J* 7.0 Hz, 3H, CH_2CH_3), 1.56 (d, *J* 6.0 Hz, 3H, $CHCH_3$), 3.20 (dq, *J* 9.6, 7.0 Hz, 1H, $CHHCH_3$), 3.41 (dq, *J* 9.6, 7.0 Hz, 1H, $CHHCH_3$), 5.53 (q, *J* 6.0 Hz, 1H, NCH), 8.08 (s, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 15.1, 21.5, 63.9, 73.1, 87.5, 108.5, 135.2. MS, *m/z* (%) 392 (33), 320 (61), 221 (21), 72 (74), 45 (100). HRMS (ES) calculated for $[M+Na]^+$ $C_7H_{10}I_2N_2NaO$: 414.8775; found 414.8768.

4-Bromo-1-(1-ethoxyethyl)-3-iodo-1*H*-pyrazole (7a). Reaction was performed in 0.037 mol scale of 4-bromo-3-iodo-1*H*-pyrazole (**7**). Purification by recrystallization from n-hexane gave the titled compound as slightly yellow crystals, yield 78.6%, 10.03 g, mp 59-60 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.04 (t, *J* 7.0 Hz, 3H, CH_2CH_3), 1.56 (d, *J* 6.0 Hz, 3H, $CHCH_3$), 3.21 (dq, *J* 9.6, 7.0 Hz, 1H, $CHHCH_3$), 3.42 (dq, *J* 9.6, 7.0 Hz, 1H, $CHHCH_3$), 5.52 (q, *J* 6.0 Hz, 1H, NCH), 8.19 (s, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 15.1, 21.4, 63.9, 87.9, 102.6, 102.7, 130.5. MS, *m/z* (%) 346 : 344 (8 : 8), 302 (11), 300 (11), 175 (10), 73 (92), 45 (100). HRMS (ES) calculated for $[M+Na]^+$ $C_7H_{10}BrIN_2NaO$: 366.8913; found 366.8916.

1-(1-Ethoxyethyl)-3-iodo-5-(trifluoromethyl)-1*H*-pyrazole (8a). Reaction was performed in 0.02 mol scale of 3-iodo-5-(trifluoromethyl)-1*H*-pyrazole (**8**). Purification by column chromatography (ethyl acetate in n-hexane) gave the titled compound as slightly yellow oil, yield 74.9%, 5 g. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.07 (t, *J* 7.0 Hz, 3H, CH_2CH_3), 1.62 (d, *J* 5.9 Hz, 3H, $CHCH_3$), 3.20 (dq, *J* 9.4, 7.0 Hz, 1H, $CHHCH_3$), 3.46 (dq, *J* 9.3, 7.0 Hz, 1H, $CHHCH_3$), 5.81 (q, *J* 5.9 Hz, 1H, NCH), 7.08 (s, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 15.1, 21.4, 26.8, 63.7, 87.1, 87.2, 114.2 (2 signals), 120.1, 122.7, 143.3, 143.7. MS, *m/z* (%) 334 (0.4), 289 (7), 262 (6), 163 (18), 73 (100), 45 (74). HRMS (ES) calculated for $[M+Na]^+$ $C_8H_{10}F_3IN_2NaO$: 356.9682; found 356.9685.

1-(1-Ethoxyethyl)-3-iodo-4-nitro-1*H*-pyrazole (9a). Reaction was performed in 0.021 mol scale of 3-iodo-4-nitro-1*H*-pyrazole (**9**). Purification by recrystallization from n-hexane : ethyl acetate mixture (10 : 1) gave titled compound as slightly yellow crystals, yield 77%, 5.01 g, mp 82-84 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.23 (t, *J* 7.1 Hz, 3H, CH_2CH_3), 1.69 (d, *J* 6.0 Hz, 3H, $CHCH_3$), 3.62 – 3.45 (m, 2H, CH_2CH_3), 5.54 (q, *J* 6.0 Hz, 1H, NCH), 8.33 (s, 1H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.8, 22.4, 65.5, 90.1, 92.5, 127.5, 139.4. MS, *m/z* (%) 311 (2), 266 (4), 223 (25), 73 (100), 45 (92). HRMS (ES) calculated for $[M+Na]^+$ $C_7H_{10}IN_3NaO_3$: 333.9659; found 333.9658.

1-(1-Ethoxyethyl)-4-iodo-3-nitro-1*H*-pyrazole (10a). Reaction was performed in 0.042 mol scale starting of 4-iodo-3-nitro-1*H*-pyrazole (**10**). Purification by recrystallization from n-hexane : ethyl acetate (10 : 1) mixture gave titled compound as slightly yellow crystals, yield 80%, 10.4 g, mp 84-85 ºC. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ: 1.07 (t, *J* 7.0 Hz, 3H, CH_2CH_3), 1.61 (d, *J* 5.9 Hz, 3H, $CHCH_3$), 3.28 (dq, *J* 9.5, 7.0 Hz, 1H, $CHHCH_3$), 3.49 (dq, *J* 9.5, 7.0 Hz, 1H, $CHHCH_3$), 5.66 (q, *J* 5.9 Hz, 1H, NCH), 8.49 (s, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ: 15.1, 21.4, 57.32, 64.5, 89.2, 138.4, 155.1. MS, *m/z* (%) 311 (9), 267 (11), 223 (2), 73 (100), 45 (80). HRMS (ES) calculated for $[M+Na]^+$ $C_7H_{10}IN_3NaO_3$: 333.9659; found 333.9654.

Ethyl 1-(1-ethoxyethyl)-3-iodo-1*H*-pyrazole-4-carboxylate (11a). Reaction was performed in 0.0188 mol scale starting from ethyl 3-iodo-1*H*-pyrazole-4-carboxylate (**11**). Purification by recrystallization from n-hexane : ethyl acetate mixture (10 : 0.5) gave titled compound as slightly yellow crystals, yield 43%, 2.67 g, mp 65-67 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.20 (t, *J* 7.0 Hz, 3H, CH_2CH_3), 1.40 (t, *J* 7.1 Hz, 3H, $COOCH_2CH_3$), 1.67 (d, *J* 6.0 Hz, 3H, $CHCH_3$), 3.57 – 3.37 (m, 2H, OCH_2CH_3), 4.38 (q, *J* 7.1 Hz, 2H, $COOCH_2CH_3$), 5.53 (q, *J* 6.0 Hz, 1H, NCH), 8.02 (s, 1H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.3, 14.8, 22.3, 60.5, 64.9, 88.7, 97.5, 118.4, 131.1, 161.7. MS, *m/z* (%) 338 (6), 294 (49), 221 (25), 167 (50), 73 (99), 45 (100). HRMS (ES) calculated for $[M+Na]^+$ $C_{10}H_{15}IN_2NaO_3$: 361.0019; found 361.0018.

1-(1-Ethoxyethyl)-3-iodo-4-methyl-1*H*-pyrazole (12a). Reaction was performed in 0.0192 mol scale starting from ethyl 3-iodo-4-methyl-1*H*-pyrazole (**12**). Purification by column chromatography (ethyl acetate in n-hexane, gradient mode) gave titled compound as yellow oil, yield 80%, 4.3 g. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.03 (t, *J* 7.0 Hz, 3H, CH_2CH_3), 1.54 (d, *J* 6.0 Hz, 3H, $CHCH_3$), 1.92 (d, *J* 0.7 Hz, 3H, CH_3), 3.17 (dq, *J* 9.5, 7.1 Hz, 1H, $CHHCH_3$), 3.39 (dq, *J* 9.5, 7.0 Hz, 1H, $CHHCH_3$), 5.45 (q, *J* 6.0 Hz, 1H, NCH), 7.69 (d, *J* 0.7 Hz, 1H, Ar-H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 11.2, 15.2, 21.6, 63.5, 86.9, 101.8, 121.1, 127.9. MS, *m/z* (%) 280 (13), 236 (34), 221 (15), 208 (39), 109 (36), 93 (11), 73 (49), 45 (100). HRMS (ES) calculated for $[M+Na]^+$ $C_8H_{13}IN_2NaO$: 302.9965; found 302.9964.

3-Bromo-1-(1-ethoxyethyl)-4-nitro-1*H*-pyrazole (13a). Reaction was performed in 0.026 mol scale starting from ethyl 3-bromo-4-nitro-1*H*-pyrazole (**13**). Purification by recrystallization from n-hexane : toluene (20 : 1) mixture gave titled compound as white crystals, yield 75%, 5.2 g, mp 59-60 ºC. ^{1}H NMR (400 MHz, DMSO-*d6*) δ: 1.08 (t, *J* 7.0 Hz, 3H, CH_2CH_3), 1.61 (d, *J* 5.9 Hz, 3H, $CHCH_3$), 3.37 – 3.27 (m, 1H, $CHHCH_3$), 3.49 (dq, *J* 9.5, 7.0 Hz, 1H, $CHHCH_3$), 5.62 (q, *J* 5.9 Hz, 1H, NCH), 9.18 (s, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 15.0, 21.1, 64.4, 88.9, 122.3, 132.7, 133.1. MS, *m/z* (%) 266 : 264 (0.2 : 0.2), 220 (6), 218 (6), 177 (10), 175 (10), 73 (100), 45 (95). HRMS (ES) calculated for $[M+Na]^+$ $C_7H_{10}BrN_3NaO_3$: 285.9798; found 285.9797.

Ethyl 3-bromo-1-(1-ethoxyethyl)-1*H*-pyrazole-4-carboxylate (14a). Reaction was performed in 0.023 mol scale starting from ethyl 3-bromo-4-nitro-1*H*-pyrazole (**13**). Purification by

recrystallization from n-hexane: toluene (20 : 1) mixture gave titled compound as white crystals, yield 82.8%, 5.5 g, mp 66-67 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.05 (t, *J* 7.0 Hz, 3H, CH_2CH_3), 1.28 (t, *J* 7.1 Hz, 3H, $COOCH_2CH_3$), 1.58 (d, *J* 5.9 Hz, 3H, $CHCH_3$), 3.23 (dq, *J* 9.5, 7.0 Hz, 1H, $OCHHCH_3$), 3.45 (dq, *J* 9.5, 7.0 Hz, 1H, $OCHHCH_3$), 4.23 (q, *J* 7.1 Hz, 2H, $COOCH_2CH_3$), 5.59 (q, *J* 5.9 Hz, 1H, NCH), 8.57 (s, 1H, Ar-H). ^{13}C NMR (101 MHz, DMSO-*d6*) δ 14.6, 15.1, 21.3, 60.5, 64.0, 87.8, 113.1, 127.3, 135.5, 161.3. MS, *m/z* (%) 292 : 290 (0.4 : 0.4), 248 (16), 246 (16), 233 (12), 231 (12), 167 (25), 73 (99), 45 (100). HRMS (ES) calculated for $[M+Na]^+$ $C_{10}H_{15}BrN_2NaO_3$: 313.0158; found 313.0156.

General synthetic procedure for the reaction of pyrazole compounds 2a, 3a and 6a with Grignard reagents.

To a suspension of magnesium (1.3 equiv) in THF (for 1 mol of magnesium 700 mL of THF were used), at the boiling temperature under argon atmosphere, ethyl bromide (1.4 equiv) was added dropwise and left to stir at same temperature for one hour. Then the reaction mixture was cooled down to given temperature and solution of starting pyrazole derivative **2a, 3a** or **6a** (1 equiv) in THF (for 1 mol of pyrazole 350 mL of THF were used) was added dropwise at same temperature. After 1 hour of stirring at the same temperature dimethylformamide (1.5 equiv) was added to the reaction mixture dropwise and left to warm to room temperature overnight. Then saturated NH_4Cl (5 equiv) solution in deionized water were added to the reaction mixture, organic layer was separated and NH_4Cl solution was extracted with dichloromethane (for 1 mol of pyrazole 0.5 L of dichloromethane were used) twice. Organic layers were combined, washed with deionized water (for 1 mol of pyrazole 0.5 L of water were used), dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. Products were purified by distillation or column chromatography.

1-(1-Ethoxyethyl)-1*H*-pyrazole-3-carbaldehyde (15). Reaction was performed in 0.00188 mol scale of 1-(1-ethoxyethyl)-3-iodo-1*H*-pyrazole (**2a**), iodo – i-PrMgBr LiBr exchange reaction was performed at 0 – +5 °C. Purification by column chromatography (ethyl acetate in n-hexane, gradient mode) gave titled product as white oil, yield 19%, 0.06 g. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.16 (t, *J* 7.0 Hz, 3H, CH_2CH_3), 1.69 (d, *J* 6.0 Hz, 3H, $CHCH_3$), 3.34 (dq, *J* 9.4, 7.0 Hz, 1H, $CHHCH_3$), 3.50 (dq, *J* 9.4, 7.0 Hz, 1H, $CHHCH_3$), 5.59 (q, *J* 6.0 Hz, 1H, NCH), 6.87 (d, *J* 2.5 Hz, 1H,Ar-CH), 7.65 (dd, *J* 2.6, 0.7 Hz, 1H, Ar-H), 9.98 (d, *J* 0.7 Hz, 1H, CHO). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.05 (t, *J* 7.0 Hz, 3H, CH2CH3), 1.64 (d, *J* 6.0 Hz, 3H, CHCH3), 3.22 (dq, *J* 9.6, 7.0 Hz, 1H, CHHCH3), 3.52 – 3.42 (m, 1H, CHHCH3), 5.70 (q, *J* 6.0 Hz, 1H, NCH), 6.84 (d, *J* 2.5 Hz, 1H, Ar-H), 8.12 (dd, *J* 2.5, 0.6 Hz, 1H, Ar-H), 9.92 (d, *J* 0.6 Hz, 1H, CHO). ^{13}C NMR (100 MHz, DMSO-*d6*) δ: 15.2, 21.7, 64.0, 87.9, 106.1, 131.2, 151.1, 187.3. MS, *m/z* (%) 168 (2), 153 (3), 139 (30), 124 (83) 73 (99), 45 (100). HRMS (ES) calculated for $[M+Na]^+$ $C_8H_{12}N_2NaO_2$: 191.0791; found 191.0790.

1-(1-Ethoxyethyl)-1*H*-pyrazole-4-carbaldehyde (16). Reaction was performed in 8.27 mol scale of 1-(1-ethoxyethyl)-4-iodo-1*H*-pyrazole (**3a**), iodo – EtMgBr exchange reaction was performed at 0 – +2 °C. Purification by distillation gave titled product as white oil, yield 72%, 1000g, bp 87 ºC at 2 mbar. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.17 (t, *J* 7.0 Hz, 3H, CH_2CH_3), 1.68 (d, *J* 6.0 Hz, 3H, $CHCH_3$), 3.38 (dq, *J* 9.4, 7.0 Hz, 1H, $CHHCH_3$), 3.50 (dq, *J* 9.4, 7.0 Hz, 1H, $CHHCH_3$), 5.55 (q, *J*

6.0 Hz, 1H, NCH), 7.98 (d, *J* 0.5 Hz, 1H, Ar-H), 8.15 (d, *J* 0.5 Hz, 1H, Ar-H), 9.90 (s, 1H, CHO). ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ: 1.05 (t, *J* 7.0 Hz, 3H, CH_2CH_3), 1.61 (d, *J* 6.0 Hz, 3H, $CHCH_3$), 3.23 (dq, *J* 9.6, 7.0 Hz, 1H, $CHHCH_3$), 3.46 (dq, *J* 9.6, 7.0 Hz, 1H, $CHHCH_3$), 5.64 (q, *J* 6.0 Hz, 1H, NCH), 8.04 (s, 1H, Ar-H), 8.66 (s, 1H, Ar-H), 9.84 (s, 1H, CHO). ^{13}C NMR (100 MHz, DMSO-*d6*) δ: 15.1, 21.6, 63.9, 87.4, 124.5, 133.8, 140.0, 185.4. MS, *m/z* (%) 168 (1), 153 (1), 124 (59), 95 (22), 73 (60), 45 (100). HRMS (ES) calculated for $[M+Na]^+$ $C_8H_{12}N_2NaO_2$: 191.0791; found 191.0793.

1-(1-Ethoxyethyl)-3-iodo-1*H*-pyrazole-4-carbaldehyde (18) and 1-(1-ethoxyethyl)-4-iodo-1*H*-pyrazole-3-carbaldehyde (17). Reaction was performed in 0.01 mol scale of 1-(1-ethoxyethyl)-3,4-diiodo-1*H*-pyrazole (**6a**) iodo – EtMgBr exchange reaction was performed at -10 – -8 °C. Purification by column chromatography (ethyl acetate in n-hexane (1:4)) gave product **18** (Rf = 0.4) as slightly yellow oil, yield 55%, 1.65 g.^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ: 1.06 (t, *J* 7.0 Hz, 3H, CH_2CH_3), 1.60 (d, *J* 6.0 Hz, 3H, $CHCH_3$), 3.25 (dq, *J* 9.6, 7.0 Hz, 1H, $CHHCH_3$), 3.47 (dq, *J* 9.6, 7.0 Hz, 1H, $CHHCH_3$), 5.64 (q, *J* 6.0 Hz, 1H, NCH), 8.60 (s, 1H, Ar-H), 9.69 (s, 1H, CHO).^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ: 15.1, 21.5, 64.1, 87.9, 100.4, 124.6, 135.4, 185.5. MS, *m/z* (%) 294 (5), 250 (62), 221 (11), 73 (100), 45 (96). HRMS (ES) calculated for $[M+Na]^+$ $C_8H_{11}IN_2NaO_2$: 316.9757; found 316.9760. And **1-(1-ethoxyethyl)-4-iodo-1*H*-pyrazole-3-carbaldehyde (17)** (Rf = 0.5) as slightly yellow oil, yield 10%, 0.3 g. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ: 1.06 (t, *J* 7.0 Hz, 3H, CH_2CH_3), 1.63 (d, *J* 6.0 Hz, 3H, $CHCH_3$), 3.24 (dq, *J* 9.6, 7.0 Hz, 1H, $CHHCH_3$), 3.47 (dq, *J* 9.5, 7.0 Hz, 1H, $CHHCH_3$), 5.68 (q, *J* 6.0 Hz, 1H, NCH), 8.37 (d, *J* 0.6 Hz, 1H, Ar-H), 9.88 (d, *J* 0.6 Hz, 1H, CHO). ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ: 15.1, 21.5, 59.6, 64.2, 88.48, 136.6, 148.3, 186.5. MS, *m/z* (%) 294 (23), 265 (21), 250 (14), 221 (7), 73 (89), 45 (100). HRMS (ES) calculated for $[M+Na]^+$ $C_8H_{11}IN_2NaO_2$: 316.9757; found 316.9760.

1-(1-Ethoxyethyl)-1*H*-pyrazole-5-carbaldehyde (1c). To a solution of protected pyrazole **1a** (644 g, 4.6 mol) in 6 L of tetrahydrofuran, under argon atmosphere, 2 L of n-BuLi (5 mol, 2.5 M in n-hexane) were added dropwise at -78 ºC and left to stir at same temperature for 1 hour. Then dimethylformamide (5.5 mol) were added to the reaction mixture (at -78 ºC) and left to warm to the room temperature, and then additionally stirred at room temperature overnight. Then reaction was cooled down to 5 ºC and 5L of saturated NH_4Cl solution in water was added, organic layer was separated, and concentrated under reduced pressure. Crude product was dissolved in 2.5 L dichloromethane and extracted with NH_4Cl solution in water (same NH_4Cl solution with was used for quenching), water layer was washed with dichloromethane (2×250 mL). Organic layers were combined and washed with deionized water (2×250 mL), dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. Purification by distillation gave titled compound as slightly yellow oil, yield 65%, 500 g, bp 56ºC at 1.3 mbar. ^{1}H NMR (400 MHz, $CDCl^3$) δ: 1.14 (t, *J* 7.0 Hz, 3H, CH_2CH_3), 1.72 (d, *J* 6.0 Hz, 3H, $CHCH_3$), 3.29 (dq, *J* 9.3, 7.0 Hz, 1H, $CHHCH_3$), 3.47 (dq, *J* 9.3, 7.0 Hz, 1H, $CHHCH_3$), 6.33 (q, *J* 6.0 Hz, 1H, NCH), 6.94 (d, *J* 2.0 Hz, 1H, Ar-H), 7.63 (d, *J* 1.9 Hz, 1H, Ar-H), 9.99 (s, Hz, 1H, CHO). ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ: 1.02 (t, *J* 7.0 Hz, 3H, CH_2CH_3), 1.64 (d, *J* 5.9 Hz, 3H, $CHCH_3$), 3.16 (dq, *J* 9.4, 7.0 Hz, 1H, $CHHCH_3$), 3.41 (dq, *J* 9.4, 7.0 Hz, 1H, $CHHCH_3$), 6.30 (q, *J* 5.9 Hz, 1H, NCH), 7.14 (d, *J* 1.9 Hz, 1H, Ar-H), 7.74 (d, *J* 1.9

Hz, 1H, Ar-H), 10.02 (s, 1H, CHO). ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ: 15.2, 21.6, 63.3, 85.3, 115.1, 140.0, 140.4, 182.0. MS, *m/z* (%) 168 (1), 153 (2), 139 (37), 124 (22), 73 (80), 45 (100). HRMS (ES) calculated for $[M+Na]^+$ $C_8H_{12}N_2NaO_2$: 191.0791; found 191.0793.

General synthetic procedure for the reaction of pyrazole compounds 2a, 3a and 5a with LDA. To dry tetrahydrofurane (for 0.019 mol of starting material 40 mL of tetrahydrofurane was used), 2.5 M n-BuLi solution in n-hexane (1.1 equiv.) was added dropwise under argon atmosphere at -78 ºC temperature, following by addition of diisopropylamine (1.2 equiv.) at -78 ºC degree and left to stir at same temperature for 30 min. Then pyrazole **2a**, **3a** or **5a** (1 equiv.) solution in tetrahydrofurane (for 0,019 mol of protected pyrazole – 5 mL of THF were used) was added to the reaction mixture at -78 ºC temperature and left to stir at the same temperature for additional 30 min. Then dimethylformamide (1.3 equiv.) solution in tetrahydrofurane (for 0.025 mol of dimethylformamide – 5 mL of THF were used) were added dropwise at -78 ºC degree and left to warm to room temperature overnight. Reaction mixture was cooled down to 5 ºC temperature and quenched with saturated NH_4Cl solution in deionized water (for 0.019 mol of starting material – 12 mL of saturated NH_4Cl solution were used). Organic layer was separated, inorganic layer was extracted with dichloromethane (3×10 mL). Organic layers were combined and washed with deionized water (2×10 mL), dried with anhydrous Na_2SO_4 and evaporated under reduced pressure.

1-(1-Ethoxyethyl)-3-iodo-1*H*-pyrazole-5-carbaldehyde (2c). Reaction was performed in 0.019 mol scale of 1-(1-ethoxyethyl)-3-iodo-1*H*-pyrazole (**2a**). Purification by recrystallization of n-hexane gave titled compound as slightly yellow crystals, yield 59%, 3.29 g, mp 70-72 ºC. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ: 1.03 (t, *J* 7.0 Hz, 3H, CH_2CH_3), 1.62 (d, *J* 5.9 Hz, 3H, $CHCH_3$), 3.20 (dq, *J* 9.4, 7.0 Hz, 1H, $CHHCH_3$), 3.43 (dq, *J* 9.4, 7.0 Hz, 1H, $CHHCH_3$), 6.25 (q, *J* 5.9 Hz, 1H, NCH), 7.32 (s, 1H, Ar-H), 9.95 (s, 1H, CHO). ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ: 15.1, 21.6, 63.6, 85.8, 97.5, 122.4, 142.2, 181.3. MS, *m/z* (%) 294 (5), 265 (7), 250 (25), 235 (5), 123 (11), 73 (100), 45 (96). HRMS (ES) calculated for $[M+Na]^+$ $C_8H_{11}IN_2NaO_2$: 316.9757; found 316.9760.

1-(1-Ethoxyethyl)-4-iodo-1*H*-pyrazole-5-carbaldehyde (3c). Reaction was performed in 0.113 mol scale of 1-(1-ethoxyethyl)-4-iodo-1*H*-pyrazole (**3a**). Purification by recrystallization from n-hexane gave titled compound as slightly yellow crystals, yield 68%, 22.6 g, mp 53-54 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.17 (t, *J* 7.0 Hz, 3H, CH_2CH_3), 1.71 (d, *J* 5.9 Hz, 3H, $CHCH_3$), 3.33 (dq, *J* 9.3, 7.0 Hz, 1H, $CHHCH_3$), 3.49 (dq, *J* 9.3, 7.0 Hz, 1H, CHHCH3), 6.48 (q, *J* 5.9 Hz, 1H, NCH), 7.72 (d, *J* 0.4 Hz, 1H, Ar-H), 9.90 (s, 1H, CHO). ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ: 1.02 (t, *J* 7.0 Hz, 3H, CH_2CH_3), 1.60 (d, *J* 5.9 Hz, 3H, $CHCH_3$), 3.18 (dq, *J* 9.4, 7.0 Hz, 1H, $CHHCH_3$), 3.41 (dq, *J* 9.4, 7.0 Hz, 1H, $CHHCH_3$), 6.34 (q, *J* 5.9 Hz, 1H, NCH), 7.88 (s, 1H, Ar-H), 9.87 (s, 1H, CHO). ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ: 15.2, 21.3, 63.5, 71.4, 85.3, 137.3, 145.9, 182.0. MS, *m/z* (%) 294 (14), 265 (2), 250 (15), 235 (4), 223 (9), 73 (94), 45 (100). HRMS (ES) calculated for $[M+Na]^+$ $C_8H_{11}IN_2NaO_2$: 316.9757; found 316.9760.

4-Bromo-1-(1-ethoxyethyl)-1*H*-pyrazole-5-carbaldehyde (5c). Reaction was performed in 0.0137 mol scale of 4-bromo-1-(1-ethoxyethyl)-1*H*-pyrazole (**5a**). Purification by column chromatography (ethyl acetate in n-hexane, gradient mode) gave titled compound as slightly yellow oil, yield 73.9%, 2.5 g. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ: 1.03 (t, *J* 7.0 Hz, 3H, CH_2CH_3), 1.61 (d,

J 5.9 Hz, 3H, $CHCH_3$), 3.22 (dq, *J* 9.5, 7.0 Hz, 1H, $CHHCH_3$), 3.43 (dq, *J* 9.5, 7.0 Hz, 1H, $CHHCH_3$), 6.31 (q, *J* 5.9 Hz, 1H, NCH), 7.92 (s, 1H, Ar-H), 9.95 (s, 1H, CHO). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 15.1, 21.3, 63.6, 85.8, 102.8, 135.6, 141.0, 180.7. HRMS (ES) calculated for $[M+Na]^+$ $C_8H_{11}BrN_2NaO_2$: 268.9896; found 268.9899.

General synthetic procedure for the ethoxyethyl group rearrangement of the compounds 1c and 3c.

To a solution of pyrazole **1c** or **3c** (1 equiv.) and trifluoroacetic acid (0.01 equiv.) in dichloromethane (for 1 mol of pyrazole - 1 L of dichloromethane were used) ethyl vinyl ether (0.1 equiv.) was added. Then reaction mixture was heated at 40 °C degree for 1-2 hours and cooled down to room temperature. Dichloromethane was washed with saturated $NaHCO_3$ solution (1 × 250 mL – for 1 L of dichloromethane) then with deionized H_2O (1 × 250 mL). Organic layer was dried with anhydrous Na_2SO_4, and evaporated under reduced pressure. Products were purified by column chromatography.

1-(1-Ethoxyethyl)-1*H*-pyrazole-3-carbaldehyde (14). Reaction was performed in 0.012 mol scale of 1-(1-ethoxyethyl)-1*H*-pyrazole-5-carbaldehyde (**1c**). Purification by column chromatography (ethyl acetate in n-hexane) gave titled compound, yield 84.3 %, 1.7 g.

1-(1-Ethoxyethyl)-4-iodo-1*H*-pyrazole-3-carbaldehyde (3c'). Reaction was performed in 0.007 mol scale of 1-(1-ethoxyethyl)-4-iodo-1*H*-pyrazole-5-carbaldehyde (**3c**). Purification by column chromatography (ethyl acetate in n-hexane) gave titled compound as slightly yellow crystals, yield 72.9 %, 1.5 g.

General synthetic procedure for the Sonogashira cross-coupling reaction.

To the solution of protected pyrazole **2a-c**, **7a**, **8a**, **12a**, **17, 18** or **10a** (1 mmol) in 2 mL of dry THF $PdCl_2(PPh_3)_2$ (14.04 mg, 0.02 mmol) and triethylamine (0.25 g, 2.5 mmol) were added. Reaction mixture was flushed with argon and acetylene (1.2 mmol) were added to the reaction mixture dropwise, following by addition of CuI (1.9 mg, 0.01 mmol) and left to stir at room temperature overnight. 5 mL of deionized water were added to the reaction mixture, organic layer was separated and product was extracted with dichloromethane (2 × 5 mL), organic layers were combined and washed with 5 mL of water, dried with anhydrous Na_2SO_4 and evaporated under reduced pressure.

***tert*-Butyl 3-(phenylethynyl)-1*H*-pyrazole-1-carboxylate (20).** *tert*-Butyl 3-iodo-1*H*-pyrazole-1-carboxylate (**2b**) was used, purification by column chromatography (ethyl acetate : n-hexane (1 : 8), Rf = 0.4) gave titled compound as white crystals, yield 64.9%, 0.174 g, mp 89-91 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.60 (s, 9H, $CH(CH_3)_3$), 6.80 (d, *J* 2.8 Hz, 1H, CH) 7.53 – 7.44 (m, 3H, Ph-CH), 7.64 – 7.58 (m, 2H, Ph-CH), 8.38 (d, *J* 2.8 Hz, 1H, CH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 27.9, 82.0, 86.2, 91.5, 112.8, 121.6, 129.4, 130.0, 132.0, 132.8, 138.6, 146.9. MS, *m/z* (%) 168 (M-Boc, 100), 139 (36), 114 (14), 84 (6). HRMS (ES) calculated for $[M+Na]^+$ $C_{16}H_{16}N_2NaO_2$: 291.1104; found 291.1103.

1-(1-Ethoxyethyl)-3-(phenylethynyl)-1*H*-pyrazole (21). 1-(1-Ethoxyethyl)-3-iodo-1*H*-pyrazole (**2a**) was used, purification by column chromatography (ethyl acetate : n-hexane (1 : 4), Rf = 0.6) gave titled compound as slightly yellow oil, yield 62.5%, 0.15 g. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.05 (t, *J* 7.0 Hz, 3H, CH_2CH_3), 1.61 (d, *J* 6.0 Hz, 3H, $CHCH_3$), 3.21 (dq, *J* 9.6, 7.0 Hz, 1H,

$CHHCH_3$), 3.44 (dq, *J* 9.6, 7.0 Hz, 1H, $CHHCH_3$), 5.58 (q, *J* 6.0 Hz, 1H, $CHCH_3$), 6.61 (d, *J* 2.4 Hz, 1H, CH) 7.47 – 7.41 (m, 3H, Ph-CH), 7.59 – 7.53 (m, 2H, Ph-CH), 8.01 (d, *J* 2.4 Hz, 1H, CH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 15.2, 21.6, 63.7, 83.6, 87.1, 89.4, 110.3, 122.4, 129.3, 129.4, 129.7, 131.7, 133.7. MS, *m/z* (%) 240 (29), 196 (33), 168 (100), 139 (20), 73 (21), 45 (58). HRMS (ES) calculated for $[M+Na]^+$ $C_{15}H_{16}N_2NaO$: 263.1155; found 263.1154.

1-(1-Ethoxyethyl)-3-(phenylethynyl)-1*H*-pyrazole-5-carbaldehyde (22). 1-(1-Ethoxyethyl)-3-iodo-1*H*-pyrazole-5-carbaldehyde (**2c**) was used, purification by column chromatography (ethyl acetate : n-hexane (1 : 4), Rf = 0.5) gave titled compound as slightly yellow crystals, yield 80%, 0.215 g, mp 64-65 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.05 (t, *J* 7.0 Hz, 3H, CH_2CH_3), 1.66 (d, *J* 5.9 Hz, 3H, $CHCH_3$), 3.24 (dq, *J* 9.4, 7.0 Hz, 1H, $CHHCH_3$), 3.46 (dq, *J* 9.4, 7.0 Hz, 1H, $CHHCH_3$), 6.32 (q, *J* 5.9 Hz, 1H, $CHCH_3$), 7.38 (s, 1H, CH) 7.49 – 7.44 (m, 3H, Ph-CH), 7.63 – 7.57 (m, 2H, Ph-CH), 10.01 (s, 1H, CHO). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 15.2, 21.6, 63.6, 81.9, 86.1, 90.3, 117.7, 121.8, 129.3, 129.8, 131.9, 134.4, 141.0, 181.8. MS, *m/z* (%) 268 (17), 239 (10), 196 (100), 139 (18), 73 (34), 45 (67). HRMS (ES) calculated for $[M+Na]^+$ $C_{16}H_{16}N_2NaO_2$: 291.1104; found 291.1103.

4-Bromo-1-(1-ethoxyethyl)-3-(phenylethynyl)-1*H*-pyrazole (23). 4-Bromo-1-(1-ethoxyethyl)-3-iodo-1*H*-pyrazole (**7a**) was used, purification by column chromatography (ethyl acetate : n-hexane (1 : 8), Rf = 0.4) gave titled compound as slightly yellow oil, yield 64%, 0.204 g. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.06 (t, *J* 7.0 Hz, 3H, CH_2CH_3), 1.60 (d, *J* 6.0 Hz, 3H, $CHCH_3$), 3.24 (dq, *J* 9.5, 7.0 Hz, 1H, $CHHCH_3$), 3.46 (dq, *J* 9.5, 7.0 Hz, 1H, $CHHCH_3$), 5.55 (q, *J* 6.0 Hz, 1H, $CHCH_3$), 7.50 – 7.42 (m, 3H, Ph-CH), 7.64 – 7.53 (m, 2H, Ph-CH), 8.35 (s, 1H, ArH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 15.1, 21.4, 64.0, 80.6, 88.1, 92.8, 97.8, 121.8, 129.4, 129.8, 130.1, 131.9, 134.4. MS, *m/z* (%) 320 : 318 (16 : 16), 248 (94), 246 (100), 194 (7), 139 (16), 73 (30), 45 (64). HRMS (ES) calculated for $[M+Na]^+$ $C_{15}H_{15}BrN_2NaO$: 341.0260; found 341.0257.

1-(1-Ethoxyethyl)-3-(phenylethynyl)-5-(trifluoromethyl)-1*H*-pyrazole (24). 1-(1-Ethoxyethyl)-3-iodo-5-(trifluoromethyl)-1*H*-pyrazole (**8a**) was used, purification by column chromatography (ethyl acetate : n-hexane (1 : 20), Rf = 0.5) gave titled compound as slightly yellow oil, yield 73%, 0.225 g. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.09 (t, *J* 7.0 Hz, 3H, CH_2CH_3), 1.63 (d, *J* 5.9 Hz, 3H, $CHCH_3$), 3.25 (dq, *J* 9.2, 7.0 Hz, 1H, $CHHCH_3$), 3.52 – 3.42 (m, 1H, $CHHCH_3$), 5.76 (q, *J* 5.9 Hz, 1H, $CHCH_3$), 7.29 (s, 1H, CH) 7.54 – 7.42 (m, 3H, Ph-CH), 7.62 – 7.56 (m, 2H, Ph-CH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 15.0, 21.7, 64.0, 81.5, 87.6, 90.7, 112.6, 121.6, 129.36, 129.44, 129.9, 131.95, 131.99, 134.3. MS, *m/z* (%) 308 (15), 264 (22), 236 (100), 188 (9), 73 (57), 45 (89). HRMS (ES) calculated for $[M+Na]^+$ $C_{16}H_{15}F_3N_2NaO$: 331.1029; found 331.1030.

1-(1-Ethoxyethyl)-4-methyl-3-(phenylethynyl)-1*H*-pyrazole (25). 1-(1-Ethoxyethyl)-3-iodo-4-methyl-1*H*-pyrazole (**12a**) was used, purification by column chromatography (ethyl acetate : n-hexane (1 : 6), Rf = 0.4) gave titled compound as slightly yellow oil, yield 69.7%, 0.177 g. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.05 (t, *J* 7.0 Hz, 3H, CH_2CH_3), 1.57 (d, *J* 6.0 Hz, 3H, $CHCH_3$), 2.11 (d, *J* 0.7 Hz, 3H, CH_3), 3.20 (dq, *J* 9.6, 7.0 Hz, 1H, $CHHCH_3$), 3.42 (dq, *J* 9.6, 7.1 Hz, 1H, $CHHCH_3$), 5.49 (q, *J* 6.0 Hz, 1H, $CHCH_3$), 7.46 – 7.41 (m, 3H, Ar-CH), 7.59 – 7.53 (m, 2H, Ar-CH). 7.81 (s, 1H, Ar-CH). ^{13}C NMR (101 MHz, DMSO-d_6) δ 9.1, 15.2, 21.6, 63.6, 82.5, 87.0, 91.9,

119.9, 122.6, 127.6, 129.3, 129.3, 131.7, 134.0. MS, *m/z* (%) 254 (21), 210 (20), 182 (100), 128 (7), 77 (4), 73 (9), 45 (30). HRMS (ES) calculated for $[M+Na]^+$ $C_{16}H_{18}N_2NaO$: 277.1311; found 277.1312.

1-(1-Ethoxyethyl)-3-(phenylethynyl)-1*H*-pyrazole-4-carbaldehyde (26). 1-(1-Ethoxyethyl)-3-iodo-1*H*-pyrazole-4-carbaldehyde (**17**) was used, purification by column chromatography (ethyl acetate : n-hexane (1 : 4), Rf = 0.4) gave titled compound as slightly yellow crystals, yield 86.2%, 0.231 g, mp 72-74 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.08 (t, *J* 7.0 Hz, 3H, CH_2CH_3), 1.63 (d, *J* 5.9 Hz, 3H, $CHCH_3$), 3.28 (dq, *J* 9.5, 7.0 Hz, 1H, $CHHCH_3$), 3.50 (dq, *J* 9.5, 7.0 Hz, 1H, $CHHCH_3$), 5.67 (q, *J* 5.9 Hz, 1H, $CHCH_3$), 7.50 – 7.45 (m, 3H, Ph-CH), 7.66 – 7.62 (m, 2H, Ph-CH), 8.75 (s, 1H, ArH), 9.95 (s, 1H, CHO). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 15.1, 21.5, 64.2, 80.8, 88.0, 93.1, 121.7, 124.7, 129.3, 130.0, 132.1, 133.8, 135.1, 184.6. MS, *m/z* (%) 268 (25), 239 (5), 209 (81), 196 (65), 195 (65), 139 (15), 73 (52), 45 (100). HRMS (ES) calculated for $[M+Na]^+$ $C_{16}H_{16}N_2NaO_2$: 291.1104; found 291.1105.

1-Methyl-3-(phenylethynyl)-1*H*-pyrazole (27). 3-Iodo-1-methyl-1*H*-pyrazole (**18**) was used, purification by column chromatography (ethyl acetate : n-hexane (1 : 4), Rf = 0.2) gave titled compound as slightly yellow oil, yield 82%, 0.15 g. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.87 (s, 3H, CH_3), 6.52 (d, *J* 2.2 Hz, 1H, CH), 7.45 – 7.40 (m, 3H, Ph-CH), 7.56 – 7.51 (m, 2H, Ph-CH), 7.78 (d, *J* 2.2 Hz, 1H, CH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 39.4, 83.7, 89.1, 110.0, 122.6, 129.3, 131.7, 132.2, 133.4, 133.8. MS, *m/z* (%) 182 (100), 154 (16), 127 (18), 91 (22), 42 (13). HRMS (ES) calculated for $[M+Na]^+$ $C_{12}H_{10}N_2Na$: 205.0736; found 205.0734.

1-(1-Ethoxyethyl)-3-nitro-4-(phenylethynyl)-1*H*-pyrazole (28). 1-(1-Ethoxyethyl)-4-iodo-3-nitro-1*H*-pyrazole (**10a**) was used, purification by recrystallization from n-hexane gave titled compound as slightly yellow crystals, yield 58%, 0.165 g, mp 108-111°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.10 (t, *J* 7.0 Hz, 3H, CH_2CH_3), 1.64 (d, *J* 5.9 Hz, 3H, $CHCH_3$), 3.38 – 3.28 (m, 1H, $CHHCH_3$), 3.53 (dq, *J* 9.5, 7.0 Hz, 1H, $CHHCH_3$), 5.70 (q, *J* 5.9 Hz, 1H, $CHCH_3$), 7.49 – 7.45 (m, 3H, Ph-CH), 7.58 – 7.53 (m, 2H, Ph-CH), 8.70 (s, 1H, CH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 15.1, 21.5, 64.6, 78.5, 89.4, 93.8, 100.1, 122.2, 129.36, 129.38, 129.8, 131.8, 135.6. MS, *m/z* (%) 285 (22), 240 (6), 213 (57), 105 (94), 73 (52), 45 (100). HRMS (ES) calculated for $[M+Na]^+$ $C_{15}H_{15}N_3NaO_3$: 308.1006; found 308.1011.

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