SYNTHESIS AND 1,3-DIPOLAR CYCLOADDITION REACTIONS OF NEW PYRAZOLO[1,5,4-*ef*][1,5]BENZODIAZEPINES

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Abstract- New pyrazolo[1,5,4-*ef*][1,5]benzodiazepines have been synthesized by condensation of 7-aminoindazole with β-keto esters, alkylation and 1,3-dipolar cycloaddition. The peri- and regioselective cycloaddition of allylpyrazolo-1,5-benzodiazepinones and 2,4,6-trimethylbenzonitrile oxide was investigated by one- and two- dimensional ^{1}H and ^{13}C NMR spectrum.

INTRODUCTION

Benzodiazepines have shown a wide scale of biological activities. Many of them are an important class of psychotherapeutic compounds.[1-4] Moreover, some imidazo[4,5,1-*jk*][1,4]benzodiazepine derivatives exhibit remarkable anti-HIV activity.[5-6] A number of pyrrolo[2,1-*c*][1,4]benzodiazepines have proven to be useful as potential anticancer drugs.[7] The 1,4-benzodiazepines condensed with heterocyclic five rings have stimulated the exploitation of the chemistry of this class of compounds. In spite of this, there has been slight interest in the synthesis of 1,5-benzodiazepine analoges,[8-14] this induces us to develop novel tricyclic and tetra cyclic structural analogous based on 1,5-benzodiazepine by the reactions of condensation of 7-aminoindazole (**1**)[15] with β-keto esters, and thereafter we studied alkylation and 1,3-dipolar cycloaddition of pyrazolo-1,5-benzodiazepines.

RESULTS AND DISCUSSION

7-Aminoindazole **(1)**[15] and β-keto ester **(2a-c)** were condensed in boiling xylene with azeotropic removal of water and xylene. The reaction afforded pyrazolo-1,5-benzodiazepines **(3a-c)** in moderate yields (40-65%). Compounds **(3a-b)** were already prepared and have been published earlier by our group.[8,9]

In order to increase the activity spectrum of the compounds **(3a-c)** and to study the reactivity of the lactam function, we have alkylated pyrazolo-1,5-benzodiazepinones **(3a-b)** with allyl bromide under phase transfer conditions. Thus, the action of allyl bromide in methylene chloride as solvent, in the presence of NaOH solution (30%) and tetrabutylammonium bromide as catalyst, takes place exclusively on the amidic nitrogen atom (Scheme 1). It is worth noting that the IR spectra of the alkyl compounds **(4a-b)** in KBr, show one CO band around 1666 and 1670 cm^{-1}, which means that the alkylation of oxygen at position six of the pyrazolo-1,5-benzdiazepinones does not take place. Besides the signals due to the pyrazolo-1,5-benzodiazepinones skeleton, the ^{1}H NMR spectra show signals corresponding the allyl protons.
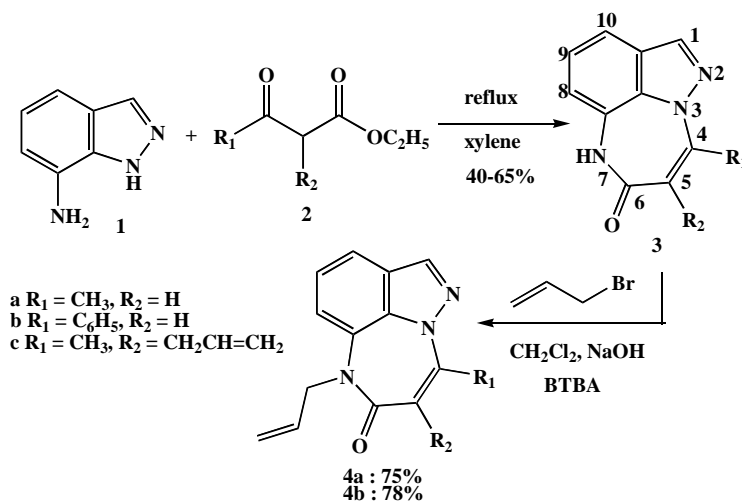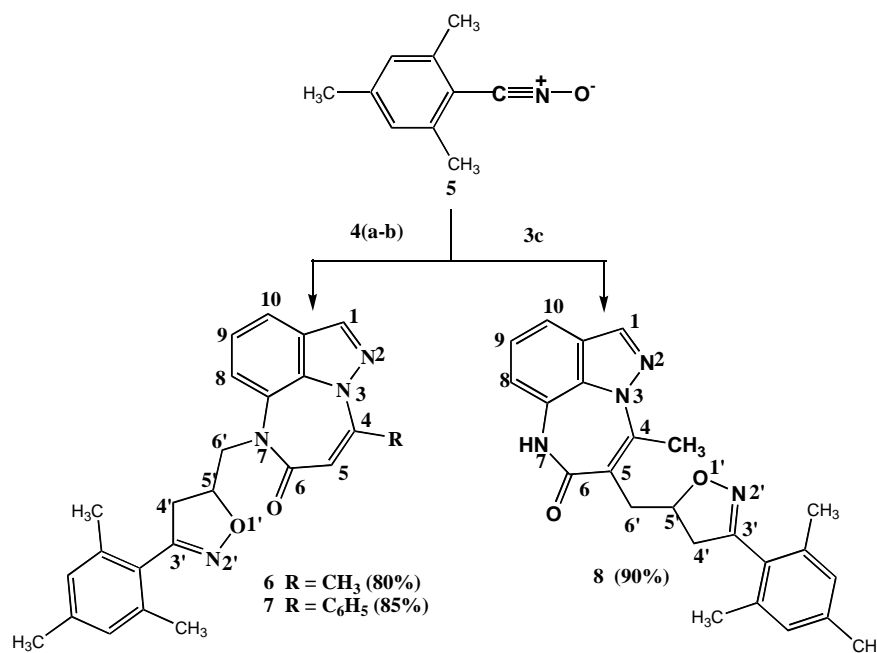

Scheme 1

It is worth noting that compound **(4b)** was evaluated *in vitro* cytotoxicity in 9 human tumour cell lines by the National Cancer Institute of Maryland, USA. It exhibited significant cytotoxicity in breast cancer cell line MDA-MB-435 (the percentage of inhibition of growth is 78% with an amount of 10^{-7} M).

With an aim of developing our research on the reactivity and the synthesis of new heterocyclic systems by 1,3-dipolar cycloaddition reaction, we report the behaviour of allylpyrazolo-1,5-benzodiazepinones **(3c)**, **(4a-b)** (HOMO) in the presence of 2,4,6-trimethylbenzonitrile oxide **(5)**[16] such as 1,3-dipole (LUMO). 1,3-Dipolar cycloaddition reactions are one of the best and more general methods for the construction of five-membered rings in a convergent and stereocontrolled manner.[17] Compounds **(3c)**, **(4a-b)** have four

potential dipolarophilic sites: C4=C5 double bond, C6=O carbonyl double bond of the benzodiazepine ring, C=C allylic double bond and C1=N2 double bond of the pyrazolic ring.

Reaction of compounds (3c), (4a-b) with 2,4,6-trimethylbenzonitrile oxide in dry benzene affords isoxazolinylmethylpyrazolo-1,5-benzodiazepines (6-8) in good yields (80-90%) (Scheme 2). No adduct resulting from condensation on one of the double bonds C4=C5, C6=O and C1=N2 was detected under the identical conditions. The reaction was exclusively periselective.

Scheme 2

The structural assignments of the isoxazolinylmethylpyrazolo-1,5-benzodiazepinones (6-8) are based on a full characterization by 250 MHz ^{1}H NMR and 63 MHz ^{13}C NMR spectra. The assignment of the signals was confirmed by additional COSY 45, NOESYTP, ^{1}H/^{13}C-correlated and DEPT spectra.

The ^{1}H NMR spectra of the compounds (6-7), show in particular a singlet at 5.28 ppm for 6 and 5.39 ppm for 7 assigned to the ethylene proton at position 5 and a signal at 7.94-7.95 ppm due to the pyrazolic proton. This excludes the addition of nitrile oxide to the double bonds C4=C5 and C1=N2.

The ^{13}C NMR spectra of cycloadducts (6-7) observe in particular a signal at 165.6 ppm for 6 and 167.4 ppm for 7 due to the carbon C-6, this excludes the addition of the dipole to the double bond C6=O.

These results demonstrate the periselectivity of the double bond allylic C=C.

The direction of the addition can also be deduced from the ^{13}C NMR spectra: the C-5'signal at 79.8-80.5 ppm slightly deshielded, rules out any other direction of the addition on the double bond allylic C=C; otherwise, the C-5' signal would appear upfield (the value would <60ppm). The reaction is thus regioselective.

The ^{1}H and ^{13}C NMR spectra of 8 exhibited all the characteristics of a bridged isoxazoline observed for 6-7. The appearance of a signal at 8.27 ppm assigned to the pyrazole ring proton in the ^{1}H NMR

spectrum as well as a C6=O carbon signal at 165.0 ppm and a signal at 108.4 ppm due to the carbon C-5 was a clear indication of the periselectivity of the reaction. The regioselectivity was also confirmed by the ^{1}H and ^{13}C NMR spectrum of **8**.

In summary, we have prepared new isoxazolinylmethylpyrazolo[1,5,4-*ef*][1,5]benzodiazepinones by 1,3-dipolar cycloaddition of 2,4,6-trimethylbenzonitrile oxide to the corresponding allylpyrazolo-1,5-benzodiazepines. These cycloaddition were found to be highly peri- and regioselective, giving the cycloadducts in good yields.

EXPERIMENTAL

General Instrumentation. Melting points were determined using a Büchi-Tottoli apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 577 spectrophotometer using KBr disks, only noteworthy IR absorptions are listed (cm^{-1}). ^{1}H and ^{13}C NMR spectra were recorded in CDCl$_3$ and DMO-d$_6$ solution (unless otherwise specified) with TMS as an internal reference using a Bruker AC 250 (^{1}H) or 62.89 MHz (^{13}C) instruments, chemical shifts are given in δ ppm downfield from TMS. Multiplicities of ^{13}C NMR resources were assigned by distortion less enhancement by polarization transfer (DEPT) experiments. MS were recorded in a Varian MAT 112 spectrometer MS. Column chromatography was carried out on SiO$_2$ (silica gel 60 Merck 0.063-0.200 mm). TLC was carried out on SiO$_2$ (silica gel 60, F 254 Merck 0.063-0.200 mm) and the spots located with UV light. All solvents were dried or purified by standard methods (D.D. Perrin, W.L.F. Armarego and D.R. Perrin *Purification of Laboratory Chemicals*; Pergamon: Oxford, 1986). Elemental analysis data were taken on a Perkin-Elmer 240C elemental analytical instrument. Commercial reagents **(2a-b)** were used without further purification unless stated. Ethyl 2-allylacetoacetate **(2c)** was prepared from commercial Ethyl acetoacetate **(2a)** by alkylation with allyl bromide.

Alkylation of Ethyl acetoacete (2a)

NaH 60% purity (860 mg, 36 mmol) was added to a solution of ethyl acetoacetate **(2a)** (2002 mg, 15.4 mmol) in anhydrous THF (50 mL) in a three-neck-round-bottom flask equipped with a thermometer and a magnetic stirring bar under an inert atmosphere. The solution was cooled to a temperature between 0-5°C and stirred for 15 min. Then an excess of allyl bromide (3630 mg, 30 mmol) was added and the solution was stirred for 3 h. The resulting mixture was allowed to come to rt and stirring was continued for 24 h. The reaction mixture was poured into ice water (100 ml) and extracted with ether (3x50 ml). The organic layers were combined and dried over anhydrous magnesium sulfate and the solvent was evaporated. The

residue was purified over silica gel column chromatography using a 70:30 mixture of methylene chloride and petroleum ether as eluent.

Yield 85%; **mp** oil; **^{1}H NMR** (CDCl$_3$): δ 1.08 (t, J = 7.4 Hz, 3H, CH$_3$), 2.26 (s, 3H, CH$_3$),2.34-2.61 (m, 2H, CH$_2$), 3.45 (m, 1H, CH), 4.05 (q, J = 7.4 Hz, 2H, CH$_2$O), 5.13 (dd, J = 3.1, 7.6 Hz, 1H, =CH$_2$), 5.35 (dd, J = 3.1, 12.6 Hz, 1H, =CH$_2$), 5.78-5.98 (m, 1H, =CH); **^{13}C NMR** (CDCl$_3$): δ 19.1 (CH$_3$), 28.6 (CH$_3$), 32.1 (CH$_2$), 61.1 (CH$_2$O), 62.5 (CH), 118.1 (=CH$_2$), 132.4 (=CH), 170.4 (CO), 201.4 (CO).

Synthesis of pyrazolo[1,5][1,5,4-*ef*]benzodiazepinone (3c)

To a solution β-keto ester **(2c)** (4250 mg, 25 mmol) and 7-aminoindazole **(1)** (2660 mg, 20 mmol) in 150 mL of xylene was added *p*-toluenesulfonic acid (0.5 mg, 2.9 10^{-3} mmol). The reaction mixture was refluxed for 6 h using an azeotropic separator. After evaporation of solvent, the residue was then purified over silica gel column chromatography using a 90:10 mixture of methylene chloride and hexane as eluent.

7*H*-5-Allyl-4-methylpyrazolo[1,5,4-*ef*][1,5]benzodiazepin-6-one (3c)

Yield 40%, yellow solid. **mp** 180-181°C (methylene chloride/ hexane); **IR**: 1670 (CO), 3010 (NH); **^{1}H NMR** (CDCl$_3$): δ 2.51 (s, 3H, CH$_3$), 3.31 (d, J = 4.7 Hz, 2H, CH$_2$), 5.05-5.18 (m, 2H, =CH$_2$), 5.85-5.98 (m, 1H, =CH), 6.49 (d, J = 7.2 Hz, 1H, Harom), 6.95 (dd, J = 7.2, 7.8 Hz, 1H, H-9), 7.03 (d, J = 7.8 Hz, 1H, Harom), 7.81 (s, 1H, H-1), 8.64 (s, 1H, NH); **^{13}C NMR** (CDCl$_3$): δ 22.9 (CH$_3$), 33.1 (CH$_2$), 118.2 (=CH$_2$), 115.7/116.8/122.6/133.8 /136.0 (5CH), 169.4 (CO); **MS** (EI) : m/z 239 (M$^+$). **Anal. Calcd** for C$_{14}$H$_{13}$N$_3$O: C, 70.28; H, 5.48; N, 17.56. Found: C, 70.38; H, 5.44; N, 17.50.

Alkylation of the pyrazolo-1,5-benzodiazepinones (3a-b)

General Procedure : To a solution the pyrazolo[1,5,4-*ef*][1,5]benzodiazepin-6-ones **(3a-b)** (10 mmol) in 50 mL of methylene chloride, the allyl bromide (2420 mg, 20 mmol) and 20 mL (1 mmol) of a solution of 30% sodium hydroxide were added. The reaction mixture was stirred at rt for 6 h. The reaction mixture was diluted and decanted. The organic layer was washed with hydrochloric acid solution (0.1 M) and then with water until neutral, and dried over calcium chloride. Methylene chloride was removed under vacuum and the residue chromatographed on silica gel column using methylene chloride as eluent.

5-7-Allyl-4-methylpyrazolo[1,5,4-*ef*][1,5]benzodiazepin-6-one (4a)

Yield 75%, yellow solid. **mp** 105-106°C (methylene chloride); **IR**: 1667 (CO) ; **^{1}H NMR** (CDCl$_3$): δ 2.37 (s, 3H, CH$_3$), 4.50-4.54 (m, 2H, CH$_2$), 5.21-5.34 (m, 2H, =CH$_2$), 5.31 (s, 1H, H-5), 5.88-6.01 (m, 1H, =CH), 6.85 (d, J = 8.5 Hz, 1H, Harom), 7.08 (dd, J = 8.5, 8.2 Hz, 1H, H-9), 7.21 (d, J = 8.2 Hz, 1H, Harom), 7.92 (s, 1H, H-1) ; **^{13}C NMR** (CDCl$_3$): δ 23.5 (CH$_3$), 51.8 (CH$_2$), 118.1 (=CH$_2$), 105.7/116.8/ 117.0/127.1/134.4/138.7 (6CH), 130.0/131.3/136.2/146.8 (4C), 166.5 (CO); **MS** (EI) : m/z 239 (M$^+$). **Anal. Calcd** for C$_{14}$H$_{13}$N$_3$O: C, 70.28; H, 5.48; N, 17.56. Found: C, 70.40; H, 5.45; N, 17.52.

5*H*-7-Allyl-4-phenylpyrazolo[1,5,4-*ef*][1,5]benzodiazepin-6-one (4b)

Yield 78%, yellow solid. **mp** 101-102°C (methylene chloride); **IR**: 1660 (CO) ; ^{1}**H NMR** (CDCl$_3$): δ 4.52-4.61 (m, 2H, CH$_2$), 5.29-5.35 (m, 2H, =CH$_2$), 5.42 (s, 1H, H-5), 5.97-6.10 (m, 1H, =CH), 7.06-7.49 (m, 8H, H-arom), 7.93 (s, 1H, H-1) ; ^{13}**C NMR** (CDCl$_3$): δ 51.8 (CH$_2$), 118.1 (=CH$_2$), 106.5/115.3/116.3 /125.5/127.9/ 129.1/129.5/132.4/137.2 (6CH), 128.1/129.4/134.8/135.3/147.1 (5C), 164.5 (CO); **MS** (EI) : m/z 301 (M$^+$). **Anal. Calcd** for C$_{19}$H$_{15}$N$_3$O: C, 75.73; H, 5.02; N, 13.94. Found: C, 75.66; H, 5.08; N, 13.90.

Reaction of 2,4,6-trimethylbenzonitrile oxide with pyrazolo-1,5-benzodiazepin-6-ones (4a-b) and (3c)

General procedure: In a 250 mL round bottomed flask equipped with thermometer and condenser was placed the pyrazolo-1,5-benzodiazepin-6-ones (1 mmol) in dry benzene (70 mL). The resulting solution was added the 2,4,6-trimethylbenzonitrile oxide **(5)** (290 mg, 1.8 mmol) and the mixture was refluxed for 4 day. Afterward, the mixture was concentrated by rotatory evaporator. Column chromatography afforded the desired isoxazolopyrazlo-1,5-benzodiazepinones in good yield.

4-Methyl-7-[3-(2,4,6-trimethylphenyl)-4',5'-dihydroisoxazol-5-ylmethyl]-5*H*-pyrazolo[1,5,4-*ef*][1,5]-benzodiazepin-6-one (6)

Column chromatography (methylene chloride/ petroleum ether 8:2) afforded **6** as yellow solid in 80% yield. **mp** 167-168°C (methylene chloride/ petroleum ether); **IR**: 1669 (CO) ; ^{1}**H NMR** (CDCl$_3$): δ 2.25 (s, 6H, 2CH$_3$), 2.28 (s, 3H, CH$_3$), 2.36 (s, 3H, CH$_3$), 3.07 (dd, J = 8.2, 17.6 Hz, 1H, H-4'), 3.37 (dd J = 10.3, 17.6 Hz, 1H, H-4'), 3.86 (dd J = 6.3, 14.3 Hz, 1H, H-6'), 4.52 (dd, J = 4.4, 14.3 Hz, 1H, H-6'), 5.11-5.17 (m, 1H, H-5'), 5.28 (s, 1H, H-5), 6.89 (s, 2H, H-arom), 7.13-7.29 (m, 3H, H-arom), 7.94 (s, 1H, H-1) ; ^{13}**C NMR** (CDCl$_3$): δ 19.9 (2CH$_3$), 21.1 (CH$_3$), 21.7 (CH$_3$), 43.3 (C-4'), 51.9 (C-6'), 78.7 (C-5'), 103.5 (C-5), 115.6/116.0/125.6/ 125.9/ 128.6/137.2 (6CH), 128.3/129.5/134.8/136.5/138.9/145.6/158.4 (7C), 167.4 (CO); **MS** (EI) : m/z 400 (M$^+$). **Anal. Calcd** for C$_{24}$H$_{24}$N$_4$O$_2$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.94; H, 6.05; N, 13.94.

4-Phenyl-7-[3-(2,4,6-trimethylphenyl)-4',5'-dihydroisoxazol-5-ylmethyl]-5*H*-pyrazolo[1,5,4-*ef*][1,5]-benzodiazepin-6-one (7)

Column chromatography (methylene chloride/ petroleum ether 8:2) afforded **(7)** as yellow solid in 85% yield. **mp** 213-214°C (methylene chloride/ petroleum ether); **IR**: 1665 (CO) ; ^{1}**H NMR** (CDCl$_3$): δ 2.28 (s, 9H, 3CH$_3$), 3.11 (dd, J = 7.2, 17.6 Hz, 1H, H-4'), 3.40 (dd, J = 10.3, 17.6 Hz, 1H, H-4'), 3.91 (dd, J = 6.6, 14.7 Hz, 1H, H-6'), 4.57 (dd, J = 4.4, 14.7 Hz, 1H, H-6'), 5.20-5.29 (m, 1H, H-5'), 5.39 (s, 1H, H-5), 6.90-7.44 (m, 10H, H-arom), 7.95 (s, 1H, H-1) ; ^{13}**C NMR** (CDCl$_3$): δ 21.7 (2CH$_3$), 22.9 (CH$_3$), 45.2 (C-4'), 53.9 (C-6'), 80.5 (C-5'), 107.8 (C-5), 117.7/118.2/127.8/129.8/130.4/131.0/137.1 (8CH), 167.4 (CO); **MS** (EI) : m/z 462 (M$^+$). **Anal. Calcd** for C$_{29}$H$_{26}$N$_4$O$_2$: C, 75.30; H, 5.67; N, 12.11. Found: C, 75.24; H, 5.65; N, 12.14.

4-Methyl-5-[3-(2,4,6-trimethylphenyl)-4',5'-dihydroisoxazol-5-ylmethyl]-7*H*-pyrazolo[1,5,4-*ef*][1,5]-benzodiazepin-6-one (8)

Column chromatography (methylene chloride) afforded **8** as yellow solid in 90% yield. **mp** 216-217°C (methylene chloride); **IR**: 1670 (CO) ; **^{1}H NMR** (DMSO-d_6): δ 2.34 (s, 6H, 2CH$_3$), 2.39 (s, 3H, CH$_3$), 2.69 (s, 3H, CH$_3$), 2.96-2.99 (m, 2H, H-6'), 3.07-3.14 (m, 2H, H-4'), 4.92-5.11 (m, 1H, H-5'), 6.85 (d, *J* = 7.1 Hz, 1H, Harom), 7.06 (s, 2H, H-Ar), 7.15 (dd, *J* = 7.1, 7.8 Hz, 1H, H-9), 7.27 (d, *J* = 7.8 Hz, 1H, Harom), 8.26 (s, 1H, H-1), 10.13 (s, 1H, NH) ; **^{13}C NMR** (DMSO-d_6): δ 19.2 (2CH$_3$), 19.3 (CH$_3$), 20.6 (CH$_3$), 35.8 (C-6'), 43.2 (C-4'), 79.8 (C-5'), 111.5/113.3/125.0/128.2/135.9 (5CH), 108.4/126.1/126.7/127.5/138.0/144.7/157.4 (7C), 165.4 (CO); **MS** (EI) : m/z 400 (M$^+$). **Anal. Calcd** for C$_{24}$H$_{24}$N$_4$O$_2$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.90; H, 6.01; N, 13.95.

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