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# Synthesis of New Tri- and Tetraheterocyclic Systems: 1,3-Dipolar Cycloaddition of Nitrilimines on 2,7-Dimethyl-4-Phenyl-3H-1,5-Benzodiazepine

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# SYNTHESIS OF NEW TRI- AND TETRAHETEROCYCLIC SYSTEMS : 1,3-DIPOLAR CYCLOADDITION OF NITRILIMINES ON 2,7-DIMETHYL-4-PHENYL-3H-1,5-BENZODIAZEPINE

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**ABSTRACT :** We report here a one-step synthesis of a new series of tri and tetraheterocyclic systems by the mixed condensation reactions of N-aryl-C-ethoxycarbonylnitrilimines and diarylnitrilimines with 2,7-dimethyl-4-phenyl-3H-1,5-benzodiazepine. This 1,3-dipolar cycloaddition is completely peri and regioselective. The structure of these products has been confirmed by $^{1}H$, $^{13}C$ NMR, mass spectroscopic and X-ray crystallographic analysis.

It has been demonstrated that heterocycles attached to nitrogenous seven membered rings, can reveal interesting biological activities[1-3]. Our research team[4-8] is interested in the synthesis and the study of regio and periselectivity of the 1,3-dipolar cycloaddition reactions on 1,2,4-triazepines, 1,5-benzodiazepines, 1,4 and 1,2-diazepines.

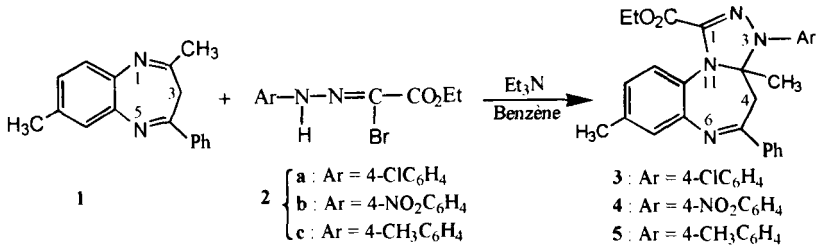
In order to develop this field of research, we have synthesized new tri and tetraheterocyclic systems by 1,3-dipolar cycloaddition of the N-aryl-C-ethoxycarbonylnitrilimines and the diarylnitrilimines on the 2,7-dimethyl-4-phenyl-3H-1,5-benzodiazepine **1**[9].

At room temperature, the 1,5-benzodiazepine **1** was treated with an equivalent of the N-aryl-C-ethoxycarbonylnitrilimines generated in situ from ethylarylhydrazono-α-bromoglyoxylate **2**[10-11] in the presence of triethylamine. We have found that in all the cases, only one type of cycloadduct **3-5** was obtained with a high yield (scheme 1).

The analysis of $^{1}H$, $^{13}C$ NMR and the mass spectra of the cycloadducts **3-5** revealed that the monocondensation happened at one of the C-N two double bands of benzodiazepine **1**.



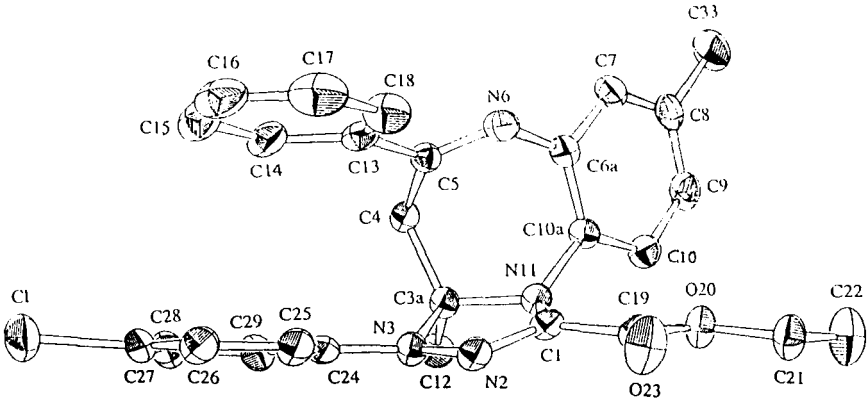
 




**Scheme 1**

This monocondensation was confirmed by the presence in $^{13}C$ NMR spectra of low intensity singlet at about 101 ppm, which is due to a quaternary $sp^3$ hybridized carbon. Furthermore the direction of the cycloaddition is unique (heteroatom of the dipole is linked to the carbon of the C-N dipolarophile site). However, all the spectroscopic data do not show which of the two dipolarophile sites ($N_1$=$C_2$ or $C_4$=$N_5$) was attacked.

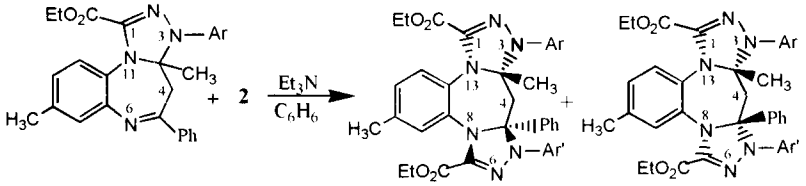
Thus, we have elucidated this periselectivity problem using the X-ray crystallographic analysis[12] which reveals unambiguously that the condensation of the dipoles happened exclusively on the $N_1$-$C_2$ dipolarophile site of the 1,5-benzodiazepine **1** (scheme 2). So, these reactions were not only periselective but regioselective as well.




**Scheme 2** : Crystalline structure of cycloadduct **3**

Afterwards, we have examined the mixed condensation reactions by treating the monocycloadducts **3-5** with an equivalent of the N-aryl-C-ethoxycarbonylnitrilimines precursors. These reactions were performed at room temperature in benzene with the presence of triethylamine providing

two mixed cycloadducts **6-9** resulting from the condensation of the dipoles on C5-N6 dipolarophile site (scheme 3).



**3** : Ar = 4-$ClC_6H_4$
**4** : Ar = 4-$NO_2C_6H_4$
**5** : Ar = 4-$CH_3C_6H_4$

**6-9a** **6-9b**

**6 a-b** : Ar = 4-$ClC_6H_4$, Ar' = 4-$NO_2C_6H_4$
**7 a-b** : Ar = 4-$NO_2C_6H_4$, Ar' = 4-$ClC_6H_4$
**8 a-b** : Ar = 4-$NO_2C_6H_4$, Ar' = 4-$CH_3C_6H_4$
**9 a-b** : Ar = 4-$CH_3C_6H_4$, Ar' = 4-$NO_2C_6H_4$

**Scheme 3**

The structures of all the new prepared compounds **6-9** were established by spectral analysis of their $^1H$, $^{13}C$ NMR and mass spectra. The $^1H$ NMR spectra of the products **6-9** present two doublets at about 3 and 4 ppm (J=14 Hz) due to two nonequivalent protons in position 4. On the other hand, the $^{13}C$ NMR spectra shows, mainly, two singlets of low intensity at about 88 and 92 ppm which are assigned to the C-3a and C-4a quaternary carbons. We notice here that the direction of this second addition was also unique; so these reactions are totally regioselective. Also, the two triazole cycles of the compounds **6-9** could adopt either cis or trans relative configuration.

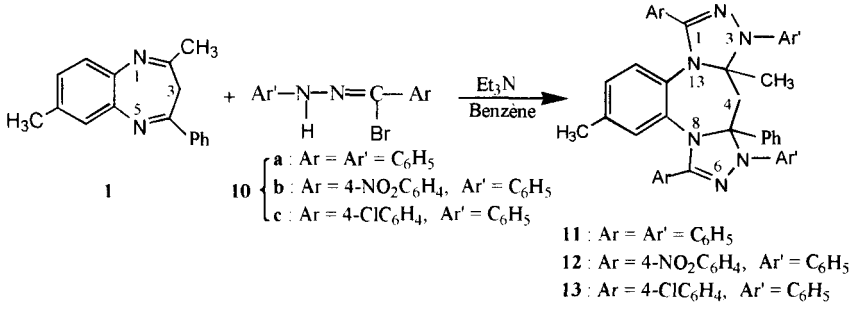
In order to determine the correct stereochemistry of these new bis triazolo-1,5-benzodiazepine, a single crystal X-ray diffraction analysis was applied over compound **7b**. Its crystal structure shows that it was in agreement with the cis configuration of the two triazole rings.

Consequently, it has been pointed out that the products **6a**, **7a** and **6b**, **7b** are respectively trans and cis isomers. As for the compounds **8a-b** and **9a-b** our attempts to separate the two isomers cis trans mixture failed. This result is perfectly in harmony with the observed result by Baouid et al.[7]

Moreover, we have studied the condensation of benzodiazepine **1** with diarylnitrilimines generated in situ by the action of triethylamine on N-phenylarylohydrazonic acid bromide **10**[13]. After stirring for 2 days at room temperature, we obtained one type of cycloadduct **11-13** (scheme 4).

The diadduct obtained, is the result of a regioselective double condensation of diarylnitrilimines on two carbon-nitrogen dipolarophile sites of benzodiazepine **1**. The structure of dicycloadducts **11-13** was determined by $^1H$, $^{13}C$ NMR and mass spectral analysis. In fact, the $^{13}C$ NMR spectra present two low intensity singlets of at about 86.50 and 87.30 ppm assigned to the to C-3a and C-4a quaternary

carbons. It is noteworthy to emphasize that we have never isolated a monocycloadduct, regardless of the quantity of the dipole used.




**Scheme 4**

In view of these facts, we can state that these reactions of condensation of the diarylnitrilimines with the 1,5-benzodiazepine **1** are completely regioselective. This result is in full accord one obtained by Aversa and al.[14] in the 1,4-diazepine series. However in each case, we obtained a mixture of inseparable diastereoisomers, in contrast with the result obtained in series the benzodiazepine of Aversa et al.[15]

## EXPERIMENTAL SECTION

Melting points were taken on a Buchi 510 apparatus and were uncorrected. The $^1$H NMR spectra were recorded with the following instruments : Bruker WP 360 CW and AC 250. TMS was used as an internal reference. The $^{13}$C NMR spectra was measured on a Varian FT 80 (20.0 MHz). Mass spectra was recorded with an JEOL JMS DX 300. Column chromatography was carried out using E-Merck silica gel.

### I/ General procedure for the condensation of N-aryl-C-ethoxycarbonylnitrilimines 2 with 1,5-benzodiazepine 1

To a solution of 1,5-benzodiazepine **1** (1.24 g, 5 mmol) and ethylarylhydrazono-α–bromoglyoxylate **2** (4.70 mmol) in benzene (20 ml), triethylamine (1.20 ml) dissolved in benzene (5 ml) was added dropwise. The mixture was stirred for 40 hours at room temperature. The mixture was washed three times with water (25 ml) and dried over anhydrous sodium sulfate. The organic layers were concentrated and the product was recrystallized in ethanol.

From **2a** (Ar=4-ClC$_6$H$_4$) is obtained :

**3-(4-chlorophenyl)-1-ethoxycarbonyl-3a,8-dimethyl-5-phenyl-3a,11-dihydro-4H-[1,2,4] triazolo[4,3-a][1,5] benzodiazepine 3**. Yield : 94.40%.

M.P. 205-206°C (Ethanol). $^1$H NMR ($CDCl_3$) : δ 1.15 (3H, t), 1.95 (3H, s), 2.45 (3H, s), 2.65, 3.45 (2H, J=14.08 Hz, 2d), 4.15 (2H, m), 6.90-7.60 (12H, m). $^{13}$C NMR ($CDCl_3$) : δ 12.75, 20.10, 27.10 ($3CH_3$), 36 (C-4), 60.40 ($CH_2O$), 101.80 (C-3a). Mass spectrum : m/z 473 (77%, $M^+$), 154 (100%).

From **2b** (Ar=4-$NO_2C_6H_4$) is obtained :

**1-ethoxycarbonyl-3a,8-dimethyl-3-(4-nitrophenyl)-5-phenyl-3a,11-dihydro-4H-[1,2,4]triazolo [4,3-a][1,5] benzodiazpine 4**. Yield 92.20%.

M.P. 208-209°C (Ethanol). $^1$H NMR ($CDCl_3$) : δ 1.10 (3H, t), 2 (3H, s), 2.45 (3H, s), 2.75, 3.75 (2H, J=14 Hz, 2d), 4.10 (2H, m), 7-8.15 (12H, m). $^{13}$C NMR ($CDCl_3$) : δ 13.90, 21.40, 27.50 ($3CH_3$), 36.70 (C-4), 62 ($CH_2O$), 101.50 (C-3a). Mass spectrum : m/z 484 (25%, $[M+H]^+$), 382 (100%).

From **2c** (Ar=4-$CH_3C_6H_4$) is obtained :

**1-ethoxycarbonyl-3a,8-dimethyl-5-phenyl-3-(4-tolyl)-3a,11-dihydro-4H-[1,2,4]triazolo[4,3-a] [1,5] benzodiazepine 5**. Yield 76.80%.

M.P. 149-151°C (Ethanol). $^1$H NMR ($CDCl_3$) : δ 1.10 (3H, t), 1.90 (3H, s), 2.20, 2.40 (6H, 2s), 2.50, 3.40 (2H, J=13.80 Hz, 2d), 4.10 (2H, m), 6.90-7.60 (12H, m). Mass spectrum : m/z 453 (100%, $[M+H]^+$).

**II/ General procedure for the condensation of N-aryl-C-ethoxycarbonylnitrilimines 2 with monocycloadduct 3-5**

To a solution of monocycloadduct (2.11 mmol) and ethylarylhydrazono-α–bromoglyoxylate **2** (2.11 mmol) in benzene (15 ml), triethylamine (1.20 ml) dissolved in benzene (5 ml) was added dropwise. The mixture was stirred for 40 hours at room temperature. The mixture was washed three times with water (25 ml) and dried over anhydrous sodium sulfate. The organic layers were concentrated and the residue was chromatographed on a silica gel column (eluent : hexane/ethyl acetate, 8/2). This produces the products **6-9**.

From **3** and **2b** (Ar`=4-$NO_2C_6H_4$) is obtained :

**3-(4-chlorophenyl)-1,7-diethoxycarbonyl-3a,10-dimethyl-5-(4-nitrophenyl)-3a,4a,8,13-tetrahydro-4H-bis[1,2,4-triazolo][4,3-a : 3',4'-d][1,5]benzodiazepine 6a** (trans). Yield 35%.

M.P. 186-188°C) (Ethanol/Dichloromethane : 9/1). $^1$H NMR ($CDCl_3$) : δ 1, 1.30 (6H, 2t), 1.90 (3H, s), 2.20 (3H, s), 3.30, 3.70 (2H, J=14 Hz, 2d), 4-4.20 (2H, m), 4.25-4.45 (2H, m), 6.40-8.30 (16H, m). $^{13}$C NMR ($CDCl_3$) : δ 14 ($2CH_3$), 20.74, 25 ($2CH_3$), 42 (C-4), 62, 62.30 ($2CH_2O$), 88 (C-3a), 91.40 (C-4a). Mass spectrum : m/z 708 (100%, $[M+H]^+$).

**3-(4-chlorophenyl)-1,7-diethoxycarbonyl-3a,10-dimethyl-5-(4-nitrophenyl)-3a,4a,8,13-tetrahydro-4H-bis[1,2,4-triazolo][4,3-a : 3',4'-d][1,5]benzodiazepine 6b** (cis). Yield 28%.

M.P. 202-204°C (Ethanol/Dichloromethane : 9/1). $^1$H NMR ($CDCl_3$) : δ 1.10-1.30 (6H, m), 1.75 (3H, s), 2.30 (3H, s), 2.55, 3.65 (2H, 2d), 4.10-4.40 (4H, m), 6.60-8.30 (16H, m). Mass spectrum : m/z 708 (38%, $[M+H]^+$), 475 (100%).

From **4** and **2a** (Ar'=4-$ClC_6H_4$) is obtained :

**5-(4-chlorophenyl)-1,7-diethoxycarbonyl-3a,10-dimethyl-3-(4-nitrophenyl)-3a,4a,8,13-tetrahydro-4H-bis[1,2,4-triazolo][4,3-a : 3',4'-d][1,5]benzodiazepine 7a** (trans). Yield 41%.

M.P. 178-180°C (Ethanol/Dichloromethane : 9/1). $^1$H NMR ($CDCl_3$) : δ 1, 1.37 (6H, 2t), 2.10 (3H, s), 2.20 (3H, s), 3.30, 3.45 (2H, J=14.20 Hz, 2d), 4.40 (4H, m), 6.70-8.10 (16H, m). $^{13}$C NMR ($CDCl_3$) : δ 14 ($2CH_3$), 21.40, 28 ($2CH_3$), 34 (C-4), 61.80, 62.20 ($2CH_2O$), 84.60 (C-3a), 86.70 (C-4a). Mass spectrum : m/z 708 (100%, $[M+H]^+$).

**5-(4-chlorophenyl)-1,7-diethoxycarbonyl-3a,10-dimethyl-3-(4-nitrophenyl)-3a,4a,8,13-tetrahydro-4H-bis[1,2,4-triazolo][4,3-a : 3',4'-d][1,5]benzodiazepine 7b** (cis). Yield 27%.

M.P. 238-239°C (Ethanol/Dichloromethane : 9/1). $^1$H NMR ($CDCl_3$) : δ 1.10-1.30 (6H, m), 1.70 (3H, s), 2.40 (3H, s), 2.55, 3.75 (2H, 2d), 4.10-4.30 (4H, m), 6.60-7.80 (16H, m). Mass spectrum : m/z 708 (35%, $[M+H]^+$), 475 (100%).

From **4** and **2c** (Ar'=4-$CH_3C_6H_4$) a mixture of two inseparable diastereoisomers (cis and trans with some proportions of 56% and 44%) was obtained :

**1,7-diethoxycarbonyl-3a,10-dimethyl-3-(4-nitrophenyl)-5-(4-tolyl)-3a,4a,8,13-tetrahydro-4H-bis[1,2,4-triazolo] [4,3-a : 3',4'-d][1,5]benzodiazepine 8**. Yield 88%.

M.P. 194-196°C (Ethanol). $^1$H NMR ($CDCl_3$) : δ 1.02, 1.10 (6H, 2t), 1.36 (6H, m), 2, 2.07, 2.20, 2.22, 2.24, 2.30 (18H, 6s), 3.17, 3.26, 3.40, 3.50 (4H, 4d), 3.95, 4.02, 4.17, 4.40 (8H, 4m), 6.60-8.10 (22H, m). $^{13}$C NMR ($CDCl_3$) : δ 13.65, 13.77, 14.12 (4 $CH_3$), 20.75, 20.84, 21.16, 21.45, 26.34 ($2CH_3$-3a, $4CH_3$Ar), 61.90, 61.98, 62.25, 62.34 ($4CH_2O$), 40.95, 41.19 (2C-4), 86.71, 87.10 (2C-3a), 93.10, 93.16 (2C-4a). Mass spectrum : m/z 688 (30%, $[M+H]^+$), 351 (100%).

From **5** and **2b** (Ar'=4-$NO_2C_6H_4$) a mixture of two inseparable diastereoisomers (cis and trans with some proportions of 82% and 18%) was obtained :

**1,7-diethoxycarbonyl-3a,10-dimethyl-5-(4-nitrophenyl)-3-(4-tolyl)-3a,4a,8,13-tetrahydro-4H-bis[1,2,4-triazolo] [4,3-a : 3',4'-d][1,5]benzodiazepine 9**. Yield 65.80%.

M.P. 135-137°C (Ethanol). $^1$H NMR ($CDCl_3$) : δ 1.30 (12H, m), 1.80 (6H, s), 2.20, 2.30 (12H, 2s), 3.30, 3.60 (4H, J=14 Hz, 2d), 4.25 (8H, m), 6.45-8.30 (22H, m). $^{13}$C NMR ($CDCl_3$) : δ 38.70, 40.87 (2 C-4), 61.66, 62.63, 62.78, 63.45 ($4CH_2O$), 87.92 (2C-3a), 90.79 (2C-4a). Mass spectrum : m/z 688 (30%, $[M+H]^+$), 149 (100%).

**III/ General procedure for the condensation of diarylnitrilimines 10 with benzodiazepine 1**

To a solution of 1,5-benzodizepine **1** (1.24 g, 5 mmol) and N-phenylarylohydrazonic acid bromide **10** (5 mmol) in benzene (30 ml), triethylamine (1.20 ml) dissolved in benzene (5 ml) was added dropwise. The mixture was stirred for two days at room temperature. The mixture was washed three times with water (25 ml) and dried over anhydrous sodium sulfate. The organic layers were concentrated and the residue was chromatographed on a silica gel column (eluent : hexane/ethyl acetate, 9.50/0.50). This produces the products **11-13**.

From **10a** (Ar=Ar'=$C_6H_5$) a mixture of two inseparable diastereoisomers (cis and trans with some proportions of 58.70% and 41.30%) was obtained :

**3a,10-dimethyl-1,3,5,7-tetraphenyl-3a,4a,8,13-tetrahydro-4H-bis[1,2,4-triazolo][4,3-a : 3',4'-d][1,5]benzodiazepine 11**. Yield 35%.

M.P. 213-215°C (Ether/Hexane : 1/9). $^1$H NMR ($CDCl_3$) : δ 1.70, 1.80 (6H, 2s), 2, 2.08 (6H, 2s), 3.30, 3.60 (4H, 2m), 6.30-7.70 (28H, m). $^{13}$C NMR ($CDCl_3$) : δ 20.50, 21, 22, 22.50 (4 $CH_3$), 37, 38 (2C-4), 86.50, 87.50 (2C-3a), 88.20, 89.50 (2C-4a). Mass spectrum : m/z 636 ( 41%, $M^+$), 324 (100%).

From **10b** (Ar=4-$NO_2C_6H_4$, Ar'=$C_6H_5$) a mixture of two inseparable diastereoisomers (cis and trans with some proportions of 81% and 19%) was obtained :

**3,10-dimethyl-3,5-diphenyl-1,7-(diparanitrophenyl)-3a,4a,8,13-tetrahydro-4H-bis[1,2,4-triazolo][4,3-a : 3',4'-d][1,5]benzodiazepine 12**. Yield 34%.

M.P. 208-210°C (Ethanol). $^1$H NMR ($CDCl_3$) : δ 1.75, 1.90, (6H, 2s), 2, 2.10 (6H, 2s), 3.40, 3.50 (4H, 2m), 6.20-8.20 (26H, m). Mass spectrum : m/z 726 (10%, $M^+$), 133 (100%).

From **10c** (Ar=4-$ClC_6H_4$, Ar'=$C_6H_5$) a mixture of two inseparable diastereoisomers (cis and trans with some proportions of 73% and 27%) was obtained :

**1,7-(diparachlorophenyl)-3a,10-dimethyl-3,5-diphenyl-3a,4a,8,13-tetrahydro-4H-bis[1,2,4-triazolo][4,3-a : 3',4'-d][1,5]benzodiazepine 13**. Yield 35%.

M.P. 230-232°C (Ether/Hexane : 2/8). $^1$H NMR ($CDCl_3$) : δ 1.60, 1.70 (6H, 2s), 2.05, 2.10 (6H, 2s), 3.20, 3.50 (4H, 2m), 6.20-7.60 (26H, m). $^{13}$C NMR ($CDCl_3$) : δ 21.50, 22.40, 23.90 (4$CH_3$), 37.50, 38.70 (2C-4), 86.10, 87.20 (2C-3a), 89.30, 89.90 (2C-4a). Mass spectrum : m/z 705 (18%, $M^+$), 358 (100%).

## REFERENCES

1- C. Bellantuono, G. Reggi, S. Garattini, G. Tognoni, Drugs, **1980**, 19, 195.

2- H. Bartsh, T. Erker, J. Heterocycl. Chem., **1988**, 25, 1151.

3- A.S. Basile, S.H. Gammal, E.A. Jones, P. Skolnick, J. Neurochem., **1989**, 53, 1057.

4- A. Baouid, A. Hasnaoui, J.-P. Lavergne, J. Heterocyclic Chem., **1991**, 28, 73.

5- M. El Messaoudi, A. Hasnaoui, M. El Mouhtadi, J.-P. Lavergne, Bull. Soc. Chim. Belg., **1992**,101 (11), 977.

6- M. El Messaoudi, A. Hasnaoui, J.-P. Lavergne, Synthetic Comm., **1994**, 24 (4), 513.

7- A. Baouid, A. Hasnaoui, A. Benharref, J.-P. Lavergne, Bull. Soc. Chim. Belg., **1994**, 103 (12), 743.

8- A. Baouid, A. Hasnaoui, J.-P. Lavergne, Bull. Soc. Chim. Belg., **1996**, 105 (6), 339.

9- J.A. Barltrop, C.G. Richards, D.M. Russel, G. Ryback, J. Chem. Soc., **1959**, 1132.

10- R. Huisgen, H.J. Koch, Ann. Chem., **1955**, 591, 200.

11- B. Sharp, C.S. Hamilton, J. Am. Chem. Soc., **1946**, 68, 588.

12- M. Essaber, A. Baouid, A. Hasnaoui, A. Benharref, M. Giorgi, M. Pierrot, Acta Cryst. **1998**, C54, 519.

13- R. Huisgen, M. Seidel, G. Wallbillich, H. Knupfer, Tetrahedron, **1962**, 17, 3.

14- M.C. Aversa, P. Bonaccorsi, P. Giannetto, D.A. Leigh, J. Heterocyclic Chem., **1989**, 26, 1619.

15- M.C. Aversa, A. Ferlazzo, P. Giannetto, F.H. Kohnke, Synthesis Comm., **1986**, 230.

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