SYNTHESIS OF POLYOXYETHYLENE BIS(3,5-SUBSTUTED PYRAZOLES)

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ABSTRACT: Bis(β-diketones) **3** obtained from bis(propargyl) polyoxyethylene ethers **1** via oxidation reactions were readily converted to polyoxyethylene bis(3,5-subsituted pyrazoles) **4** in presence of hydrazine.

Keywords: *Pyrazoles, Hydrazine hydrate, 1,3-diketones, Dipropargyl polyoxyethylene ethers, Bispyrazoles.*

INTRODUCTION

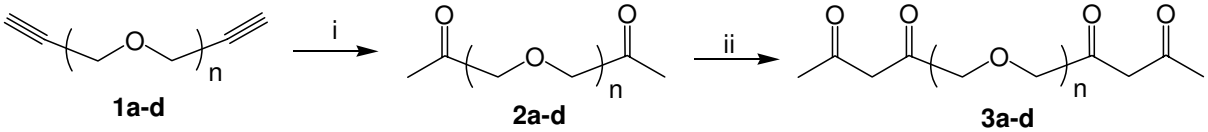
Compounds containing pyrazole moiety as a core structure exhibit a wide range of biological activities [1-7]. These include blockbuster drugs such as Celebrex [8] and Viagra [9]. Recently, the activity of a series of pyrazole-based inhibitors of p38 mitogen-activated (MAP) kinase has been reported [10]. The large applications of such heterocycles in pharmaceutical [11], as well as in agrochemical industry [12] have made them popular synthetic targets [13]. The convenient method for the synthesis of these heterocycles involves either the intermolecular [3+2] cycloadditions of 1,3-dipoles to alkynes or condensation of hydrazine with 1,3-diketones or their equivalents [14].

In general, well-designed 1,3-diketones (or diketo esters) as the precursors and 1,3-dipolar cycloaddition process have been used to produce many pyrazole compounds [15]. However, unsymetric 1,3-diketones often give a mixture of two regioisomers in a ratio which depends on the nature of 1,3-diketones [16].

In order to evaluate the synthetic possibilities of bis(propargyl) polyoxyethylene ethers that we have previously prepared [17], we describe herein a simple regioselective synthesis of new polyoxyethylene bis(3,5-substitued pyrazoles) **4** using bis(β-diketones) **3** as intermediates.

RESULTS AND DISCUSSION

Bis(β-diketones) **3** have been prepared according to methodology based on a sequential pathway shown in Scheme 1. This method is more simple than that described by Alberts et al. [18] and involves acid hydrolysis of polyoxyethylene bis(propargyl) ethers [17] **1**, leading to diketones **2** in 45-83 % yield. The reaction of ethyl acetate with these diketones afforded the corresponding bis(β-diketones) **3** in moderate yields (Table I).



n	2	3	4	5
2, 3	**a**	**b**	**c**	**d**

i: Hg^{2+}/H_3O^+; ii: 1) Et_2O Na/EtOH 2) AcOEt.

Scheme 1

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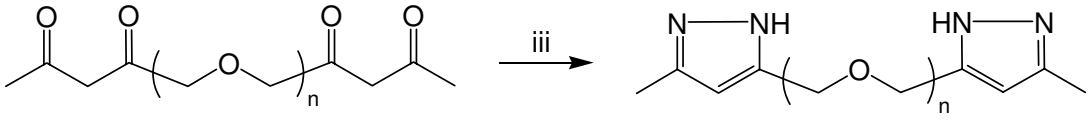
Table I: Synthesized diketones **2** and bis(β-diketones) **3**.

n	Diketones **2**	Yield (%)	$T_{éb}$ (°C/mmHg)	Bis(β-diketones) **3**	Yield (%)
2	**2a**	45	40/0,9	**3a**	60
3	**2b**	59	73/0,4	**3b**	62
4	**2c**	68	110/0,5	**3c**	70
5	**2d**	83	140/0,35	**3d**	75

Treatment of bis(β-diketones) **3** with aqueous hydrazine gave polyoxyethylene bis(pyrazoles) **4** in 60-80 % yields (Scheme 2, Table II). All products were fully characterized by their ^{1}H and ^{13}C NMR and HRMS spectra.



3a-d **4a-d**

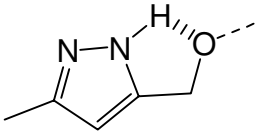
n = 2- 5. iii: $N_2H_4.H_2O$/MeOH/HClcc (reflux) 24 h.

Scheme 2

Table II: Synthesized polyoxyethylene bis(pyrazoles) **4**.

n	Bis(pyrazole) **4**	Yield (%)
2	**4a**	70
3	**4b**	72
4	**4c**	75
5	**4d**	80

The selective formation of the tautomer **4** may be interpreted on the basis of the chemical shift of the signal at 8.6 (vs. ~ 12.6 ppm for the other possible tautomers [19]) assigned to the NH proton that forms the intramolecular hydrogen bonding with the neighboring oxygen atom of the polyoxyethylene chain (Scheme 3), as evidenced by ^{1}H NMR.



Scheme 3

CONCLUSION

A series of polyoxyethylene bis(pyrazoles) has been prepared from the corresponding (β-diketones). As expected for compounds having either pyrazole moieties [20-22] or a tunable polyoxyethylene chain [23-25], these new heterocyclic compounds that contain both groups may present interesting biological properties and could also be used as potential coordinating ligands.

Potential synthetic possibilities may be predicted if we consider different heterocyclic ring formation from condensation of substituted hydrazines, (*Z*)-3-amino-2-enenitriles [26], nitrones [27] on 1,3-diketones (**3a-d**).

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on a Brüker AC 300 spectrometer at 300 and 75 MHz respectively, using TMS as standard reference. HRMS spectra in chemical ionization mode were carried out on a MAT 95 SBE spectrometer.

Synthesis of diketones 2a-d and bis(β-diketones) 3a-d.

Compounds **2** and **3** were prepared following methods described in the literature for related compounds [28]. Spectral data obtained for **2** and **3** are given below.

Spectral data of compounds 2a-d.

2a: ^{1}H NMR ($CDCl_3$): δ = 2.23 (s, 6H, $2CH_3$-), 3.47 (s, 4H, $2CH_2$-O), 4.14 (s, 4H, CH_2-CO); ^{13}C NMR ($CDCl_3$): δ = 25.6 (s, 2C, $\underline{C}H_3$-), 69.7 (s, 2C, $\underline{C}H_2$-O), 77.0 (s, 2C, $\underline{C}H_2$-CO), 206.1 (s, 2C, $\underline{C}O$) ppm.

2b: ^{1}H NMR ($CDCl_3$): δ = 2.10 (s, 6H, $2CH_3$-), 3.53-3.70 (m, 8H, $4CH_2$-O), 4.20 (s, 4H, CH_2-CO); ^{13}C NMR ($CDCl_3$): δ = 24.9 (s, 2C, $\underline{C}H_3$-), 69.8-70.0 (m, 4C, $\underline{C}H_2$-O), 77.5 (s, 2C, $\underline{C}H_2$-CO), 206.2 (s, 2C, $\underline{C}O$) ppm.

2c: ^{1}H NMR ($CDCl_3$): δ = δ 2.15 (s, 6H, $2CH_3$-), 3.53-3.70 (m, 12H, $6CH_2$-O), 4.21 (s, 4H, CH_2-CO); ^{13}C NMR ($CDCl_3$): δ = 25.6 (s, 2C, $\underline{C}H_3$-), 70.0-71.0 (m, 6C, $\underline{C}H_2$-O), 77.4 (s, 2C, $\underline{C}H_2$-CO), 206.9 (s, 2C, $\underline{C}O$) ppm.

2d: ^{1}H NMR ($CDCl_3$): δ = 2.14 (s, 6H, $2CH_3$-), 3.34-3.75 (m, 16H, $2CH_2$-O), 4.20 (s, 4H, CH_2-CO); ^{13}C NMR ($CDCl_3$): δ = 25.3 (s, 2C, $\underline{C}H_3$-), 69.5-71.0 (m, 8C, $\underline{C}H_2$-O), 77.8 (s, 2C, $\underline{C}H_2$-CO), 206.3 (s, 2C, $\underline{C}O$) ppm.

Spectral data of compounds 3a-d.

3a: ^{1}H NMR ($CDCl_3$): δ = 1.95 (s, 6H, $2CH_3$-), 2.65 (m, 4H, $2CO\text{-}CH_2$-CO), 3.40 (s, 4H, $2CH_2$-O), 3.75 (s, 4H, $2CH_2$-CO); ^{13}C NMR ($CDCl_3$): δ = 28.9 (s, 2C, $\underline{C}H_3$-), 61.4 (s, 2C, CO-$\underline{C}H_2$-CO), 71.2 (s, 2C, $\underline{C}H_2$-O), 76.6 (s, 2C, $\underline{C}H_2CO$), 206.7 (s, 2C, $CH_3\underline{C}O$), 211.8 (s, 2C, $\underline{C}O$) ppm.

3b: ^{1}H NMR ($CDCl_3$): δ = 1.92 (s, 6H, $2CH_3$-), 2.64 (s, 4H, $2CO\text{-}CH_2$-CO), 3.38 (m, 8H, $4CH_2$-O), 3.74 (s, 2C, O-CH_2-CO); ^{13}C NMR ($CDCl_3$): δ = 29.2 (s, 2C, $\underline{C}H_3$-), 61.9 (s, 2C, CO-$\underline{C}H_2$-CO), 71.8 (s, 4C, $\underline{C}H_2$-O), 75.7 (s, 2C, $\underline{C}H_2CO$), 207.1 (s, 2C, $CH_3\underline{C}O$), 212.2 (s, 2C, $\underline{C}O$) ppm.

3c: ^{1}H NMR ($CDCl_3$): δ = 1.93 (s, 6H, $2CH_3$-), 2.63 (m, 4H, $COCH_2CO$), 3.38 (m, 12H, $6CH_2$-O), 3.74 (s, 2C, O-CH_2-CO); ^{13}C NMR ($CDCl_3$): δ = 28.9 (s, 2C, $\underline{C}H_3$-), 62.3 (s, 2C, CO-$\underline{C}H_2$-CO), 72.1 (s, 6C, $\underline{C}H_2$-O), 75.8 (s, 2C, $\underline{C}H_2CO$), 207.9 (s, 2C, $CH_3\underline{C}O$), 212.7 (s, 2C, $\underline{C}O$) ppm.

3d: ^{1}H NMR ($CDCl_3$): δ = 1.1.93 (s, 6H, $2CH_3$-), 2.64 (m, 4H, $COCH_2CO$), 3.39 (m, 16H, $8CH_2$-O), 3.76 (s, 2C, O-CH_2-CO); ^{13}C NMR ($CDCl_3$): δ = 28.6 (s, 2C, $\underline{C}H_3$-), 61.4 (s, 2C, CO-$\underline{C}H_2$-CO), 71.2 (s, 8C, $\underline{C}H_2$-O), 77.2 (s, 2C, $\underline{C}H_2CO$), 208.4 (s, 2C, $CH_3\underline{C}O$), 213.2 (s, 2C, $\underline{C}O$) ppm.

Synthesis of bis(pyrazole) polyoxyethylene ethers (4):

General procedure: To a stirred solution of β-diketone **3** (10 mmol) in methanol (8 mL) and 0.5 mL concentrated hydrochloric acid, aqueous hydrazine (0.1 mol) in methanol (8 mL) was slowly added at room temperature. The mixture was refluxed for 24 h. Solvent was evaporated and the crude product purified by silica gel column chromatography, using the mixture ($MeOH/CHCl_3$: 75/25) as eluant to obtain pure polyoxyethylene bis(pyrazol) **4** as viscous oils.

1,2-bis((3-methyl-1H-pyrazol-5-yl)methoxy)ethane (**4a**): ^{1}H NMR ($CDCl_3$): δ = 2.3 (s, 6H, $2CH_3$-), 3.3-3.7 (m, 4H, $2CH_2$-O), 4.2 (s, 4H, O-CH_2-C=); 6.2 (s, 2H, CH=C), 8.9 (l.s., 2H, NH); ^{13}C NMR ($CDCl_3$): δ = 11.3 (s, 2C, $\underline{C}H_3$-), 70.5 (s, 2C, O-$\underline{C}H_2$-C=), 68.6-72.6 (2s, 2C, $\underline{C}H_2$-O), 101.1 (s, 2C, $\underline{C}H$=), 147.9 (s, 2C, CH_3-$\underline{C}$=N), 155.5 (s, 2C, C=$\underline{C}$-N) ppm; HRMS Calc.: 250.14308, found: 250.14367, Δ(mmu) = 0.6.

5,5'-(2,2'-oxybis(ethane-2,1-diyl)bis(methylene)bis(3-methyl-1H-pyrazole) (**4b**): ^{1}H NMR ($CDCl_3$): δ = 2.4 (s, 6H, $2CH_3$-), 3.2-3.5 (m, 8H, CH_2-O), 4.1 (s, 4H, O-CH_2-C=); 5.9 (s, 2H, CH=C), 8.6 (l.s., 2H, NH); ^{13}C NMR ($CDCl_3$): δ = 11.23 (s, 2C, $\underline{C}H_3$-), 71.6 (s, 2C, O-$\underline{C}H_2$-C=), 68.5-72.6 (2s, 4C, -$\underline{C}H_2$-O), 101.2 (s, 2C, $\underline{C}H$=), 147.96 (s, 2C, CH_3-$\underline{C}$=N), 155.34 (s, 2C, C=$\underline{C}$-N) ppm; HRMS Calc.: 294.16929, found: 294.16967, Δ(mmu) = 0.4.

1,12-bis(3-methyl-1H-pyrazol-5-yl)-2,5,8,11-tetraoxadodecane (**4c**): ^{1}H NMR ($CDCl_3$): δ = 2.28 (s, 6H, $2CH_3$-), 3.25-3.6 (m, 12H, CH_2-O), 4.1 (s, 4H, O-CH_2-C=), 6.3 (s, 2H, CH=C), 8.86 (l.s., 2H, NH); ^{13}C NMR ($CDCl_3$): δ = 11.3 (s, 2C, $\underline{C}H_3$-), 70.5 (s, 2C, O-CH_2-C=), 68.6-72.6 (2s, 6C, -$\underline{C}H_2$-O), 100.8 (s, 2C, CH=), 147.6 (s, 2C, CH_3-$\underline{C}$=N), 155.2 (s, 2C, C=$\underline{C}$-N) ppm; HRMS Calc.: 338.19552, found: 338.19521, Δ(mmu) = -0.3.

1,15-bis(3-methyl-1H-pyrazol-5-yl)-2,5,8,11,14-pentaoxapentadecane (**4d**): ^{1}H NMR ($CDCl_3$): δ = 2.28 (s, 6H, $2CH_3$-), 3.25-3.6 (m, 14H, CH_2-O), 4.2 (s, 4H, O-CH_2-C=), 6.3 (s, 2H, CH=C), 8.86 (l.s., 2H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 11.4 (s, 2C, $\underline{C}H_3$-), 70.6 (s, 2C, O-CH_2-C=), 68.6-72.6 (2s, 6C, -$\underline{C}H_2$-O), 100.8 (s, 2C, CH=), 147.6 (s, 2C, CH_3-$\underline{C}$=N), 155.2 (s, 2C, C=$\underline{C}$-N) ppm; HRMS Calc.: 382.22172, found: 382.22241, Δ(mmu) = 0.7.

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REFERENCES

[1] J. Elguero, A. R. Katritzky, C. W. Rees, E. F. V. Scriven, *Comprehensive Heterocyclic Chemistry II*; Pergamon-Elsevier Science: Oxford, **1996**.
[2] M. Sutharchanadevi, R. Murugan, A. R. Katritzky, C. W. Rees, E. F. V. Scriven, *Comprehensive Heterocyclic Chemistry II*; Pergamon-Elsevier Science: Oxford, **1996**.
[3] P. Pevarello, M. G. Brasca, P. Orsini, G. Traquandi, A. Longo, M. Nesi, F. Orzi, C. Piutti, P. Sansonna, M. Varasi, A. Cameron, A. Vulpetti, F. Roletto, R. Alzani, M. Ciomei, C. Albanese, W. Pastori, A. Marsiglio, E. Pesenti, F. Fiorentini, J. R. Bischoff, C. Mercurio, *J. Med. Chem.,* **2005**, *48*, 2944.
[4] S. K. Singh, P. G. Reddy, K. S. Rao, B. B. Lohray, P. Misra, S. A. Rajjak, Y. K. Rao, A. Venkateswarlu, *Bioorg. Med. Chem. Lett.,* **2004**, *14*, 499.
[5] J. S. Sawyer, B. D. Anderson, D. W. Beight, R. M. Campbell, M. L. Jones, D. K. Herron, J. W. Lampe, J. R. McCowan, W. T. McMillen, N. Mort, S. Parsons, E. C. R. Smith, M. Vieth, L. C. Weir, L. Yan, F. Zhang, J. M. Yingling, *J. Med. Chem.,* **2003**, *46*, 3954.
[6] F. Chimenti, A. Bolasco, F. Manna, D. Secci, P. Chimenti, O. Befani, P. Turini, V. Giovannini, B. Mondovi, R. Cirilli, F. L. Torre, *J. Med. Chem.,* **2004**, *47*, 2071.
[7] S. R. Stauffer, C. J. Coletta, R. Tedesco, G. Nishiguchi, K. Carlson, J. Sun, B. S. Katzenellenbogen, J. A. Katzenellenbogen, *J. Med. Chem.,* **2000**, *43*, 4934.
[8] T. D. Penning, J. J. Talley, S. R. Bertenshaw, J. S. Carter, P. W. Collins, S. Docter, M. J. Graneto, L. F. Lee, J. W. Malecha, J. M. Miyashiro, R. S. Rogers, D. J. Rogier, S. S. Yu, G. D. Anderson, E. G. Burton, J. N. Cogburn, S. A. Gregory, C. M. Koboldt, W. E. Perkins, K. Seibert, A. W. Veenhuizen, Y. Y. Zhang, P. C. Isakson, *J. Med. Chem.,* **1997**, *40*, 1347.
[9] N. K. Terrett, A. S. Bell, D. Brown, P. Ellis, *Bioorg. Med. Chem. Lett.*, **1996**, *6*, 1819.
[10] M. J. Graneto, R. G. Kurumbail, M. L. Vazquer, H. -S. Shieh, J. L. Pawlitz, J. M. Williams, W. C. Stallings, L. Geng, A. S. Narain, F. J. Koszyk, M. A. Stealey, X. D. Xu, R. M. Weier, G. J. Hanson, R. J. Mourey, R. P. Compton, S. J. Mnich, G. D. Anderson, J. B. Monahan, R. Devraj, *J. Med. Chem.,* **2007**, *50*, 5712.
[11] S. Tobiishi, T. Sasada, Y. Nojiri, F. Yamamoto, T. Mukai, K. Ishiwata, M. Maeda, *Chem. Pharm. Bull.*, **2007**, *55*, 1213.
[12] K. Y. Lee, J. M. Kim, J. N. Kim, *Tetrahedron Lett.* **2003**, *44*, 6737 and references therein.
[13] J.-P. Vors, V. Gerbaud, N. Gabas, J. P. Canselier, N. Jagerovic, M. L. Jimenoc, J. Elguero, *Tetrahedron,* **2003**, *59*, 555.
[14] B. C. Bishop, K. M. J. Brands, A. D. Gibb, D. J. Kennedy, *Synthesis*, **2004**, *1*, 43.
[15] V.Montoya, J. Pons, V. Branchadell, J. Ros, *Tetrahedron,* **2005**, *61*, 12377.

[16] A. Tanitame, Y. Oyamada, K. Ofuji, M. Fujimoto, N. Iwai, Y. Hiyama, K. Suzuki, H. Ito, H. Terauchi, M. Kawasaki, K. Nagai, M. Wachi, J. Yamagishi, *J. Med. Chem.,* **2004**, *47*, 3693.
[17] N. Mekni, A. Baklouti, *J. Soc. Chim. Tunisie*, **2005**, *7*, 205.
[18] A. H. Alberts, D. J. Cram, *J. Am. Chem. Soc.,* **1979**, *101*, 3545.
[19] E. J. Michael, S. -J. Min, K. N. Houk, D. Ess, *J. Org. Chem.,* **2004**, *69*, 9085.
[20] Q. Han, C. H. Chang, R. Li, Y. Ru, P. K. Jadhav, P. Y. S. Lam, *J. Med. Chem.*, **1998**, *41*, 2019.
[21] A. A. Nikitenko, M. W. Winkley, J. Zeldis, K. Kremer, A. W. -Y. Chan, H. Strong, M. Jennings, I. Jirkovsky, D. Blum, G. Khafizova, G. T. Grosu, A. M. Venkatesan, *Org. Process Res. Dev.,* **2006**, *10*, 712.
[22] S. Nieto, J. Pérez, L. Riera, V. Riera, D. Miguel, J. A. Golen, A. L. Rheingold, *Inorg. Chem.*, **2007**, *46*, 3407.
[23] N. Higashi, M. Yamauchi, Y. Okumura, M. Nakanishi, J. Sunamoto, *J. Biochim. Biophys. Acta,* **1996**, *1285*, 183.
[24] E. Söderlind, M. Wollbratt, C. Von Corswant, *Int. J. Pharm.,* **2003**, *252*, 61.
[25] B. Klajnert, W. Walach, M. Bryszewska, A. Dworak, D. Shcharbin, *Cell. Biology Int.,* **2006**, *30*, 248.
[26] Y. Yamaguchi, I. Katsuyama, K. Funabiki, M. Matsui, K. Shibita, *Heterocyclic Chem.*, **1998**, *35*, 805.
[27] A. Loupy, A. Petit, D. Bonnet-Delpon, *J. Fluorine Chem.*, **1995**, *75*, 215.
[28] B. S. Furiss, A. J. Hannford, P. W. G. Smith, A. R. Tatchell, *Practical Organic Chemistry*, 5th ed., London, **1989**.