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Research Article

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Polyethylene glycol (PEG-400) as an efficient and recyclable reaction media for the synthesis of substituted 4-(1-aryl-2-nitroethyl)-3-methyl-1H-pyrazol-5-ol in catalyst free conditions

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ABSTRACT

Polyethylene glycol (PEG-400) was found to be an effective reaction medium for the one-pot synthesis of 4-(1-aryl-2-nitroethyl)-3-methyl-1H-pyrazol-5-ol derivatives in good yields under mild reaction conditions. The use of PEG-400 makes this method low cost, recyclable, and eco-friendly.

Keywords*:* Michael addition, Catalyst-free conditions, Pyrazole, Hetero cyclic, styrene, Polyethylene glycol.

INTRODUCTION

The fast and effective relief of pain and inflammation in the human being is continued to be a major challenge in the medicinal chemistry researchers. Non-steroidal anti-inflammatory drugs (NSAIDs) are important therapeutic agents for the alleviation of pain and inflammation associated with a number of pathological conditions [1].Moreover the pyrozole moiety is present in a wide variety of biologically active compounds, such as anticancer [2a], antimicrobial [2b] anti-inflammatory [2c], insecticidal [2d], and molluscicidal activities [2e,f], they are also potential inhibitors of human Chk1 kinase. Due to their biological significance [2] . In the last decade several pyrazole derivatives are proved to have potent anticancer activity by the inhibition of cyclin-dependent kinases. (CD Ks). CDKs are members of the large family of protein kinases and are responsible for the eukariotic cell cycle regulation; they are intensively studied for their cancer implication [3-7] .These compounds known to exhibit as antimicrobial [8,9], antiviral [10,11] and anticancer [12,13] agents after the discovery of natural pyrazole C-glycoside pyrazofurin 4-hydroxy-3-b-D-ribofuranosyl-1H-pyrazole -5-carboxamide (Fig. 1).

In recent years, the use of alternative solvents such as ionic liquids, polyethylene glycol, and super critical fluids has gained importance as green reaction media in view of environmental perception [14,15]. Though water is a safe alternative, it is not always possible to use water as a solvent due to hydrophobic nature of the reactants and the sensitivity of many catalysts to aqueous conditions [16] .In this context, PEG has become as an alternative reaction media to perform organic synthesis due to its inherent advantages over toxic solvents. Furthermore, PEG is inexpensive, easy to handle, thermally stable, non-toxic, and recyclable. To the best of our knowledge, there are no reports for the synthesis of 4-(1-aryl-2-nitroethyl)-3-methyl-1H-pyrazol-5-ol using PEG-400 as a reaction medium under catalyst-free conditions.

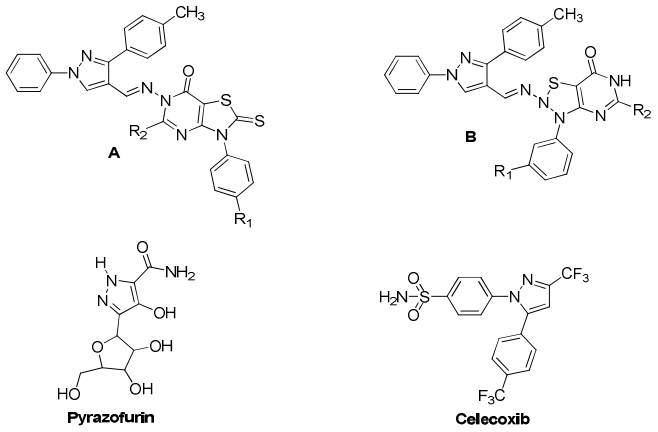
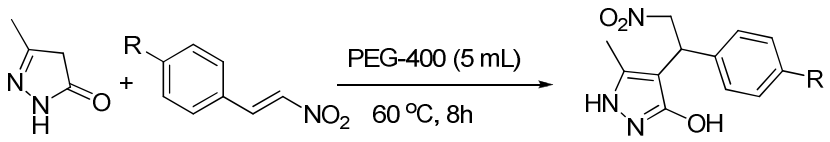


Fig 1. Sructure of celecoxib, pyrazofurin and of pyrazole A and B

In continuation of our interest on PEG mediated organic transformations [17] we, herein report a simple and efficient approach for the synthesis of 4-(1-aryl-2-nitroethyl)-3-methyl-1H-pyrazol-5-ol under catalyst-free conditions using PEG-400 as an ecofriendly and recyclable medium (Scheme 1).



Scheme 1 Preparation of 4-(1-aryl-2-nitroethyl)-3-methyl-1H-pyrazol-5-ol

In general, all the reactions are clean affording the *4-(1-aryl-2-nitroethyl)-3-methyl-1H-pyrazol-5-ol* derivatives in high yields under the above conditions. Both electron rich and electron-deficient aldehyde derivatives gave the desired products (Table 1). The structure of all the products were determined from their spectral (IR, ^{1}H NMR, ^{13}C NMR and ESI-MS) data and also by direct comparison with authentic samples [18].

In general, all the reactions were clean affording the *4-(1-aryl-2-nitroethyl)-3-methyl-1H-pyrazol-5-ol* derivatives in good yields under the above conditions (Table 1). The substituent had shown some effect on conversion. Having optimized reaction condition in hand, we were interested to study the electronic effect of substituents on aromatic ring of β-nitrostyrenes. As we envisaged, β- nitro styrene bearing electron withdrawing groups such as bromo, chloro and fluoro gave expected products in good yield where as β-nitrostyrene bearing electron donating groups such as methoxy, methyl required longer reaction time to give the corresponding Michael adducts with comparable yield. Interestingly, mono-aldol reaction was observed in case of 2, 6- dimethylpyridine. No bis-adduct was isolated under the present reaction conditions (Entries 3a-3p Table 1). The structures of all the products were determined from their spectral (IR, ^{1}H NMR, ^{13}C NMR, and ESI-MS) data and also by direct comparison with authentic samples[14]. The scope of this process was illustrated with respect to various nitro styrenes and 3-methyl-1H-pyrazol-5(4H)-one (Table 1). The generality of this reaction was investigated and the results are presented in Table 1. As seen in Table 1, a variety of nitrostyrenes underwent smooth condensation with 3-methyl-1H-pyrazol-5(4H)-one in PEG-400at 60^{O}C to provide a diversified *4-(1-aryl-2-nitroethyl)-3-methyl-1H-pyrazol-5-ol* (Table 1)19. A plausible reaction mechanism is depicted in Scheme 2. PEG-400 activates nitro styrene. Subsequent attack of the pyrazole group on nitrostyrene, gave the desired *4-(1-aryl-2-nitroethyl)-3-methyl-1H-pyrazol-5-ol* derivatives (Scheme 2).

Scheme 2. Michael addition of 3-methyl-2-pyrazolin-5-one to the β-nitrostyrenes

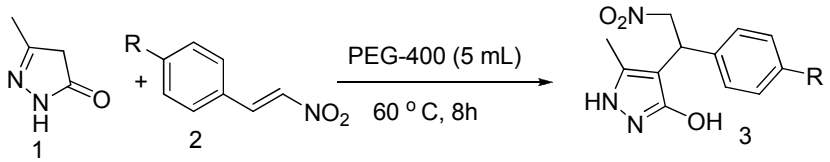
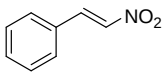
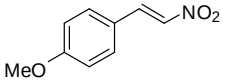
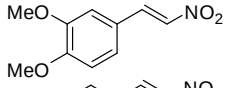
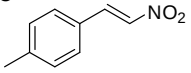
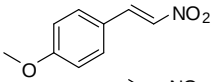
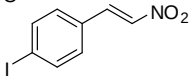
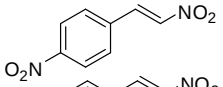
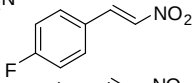
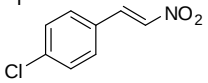
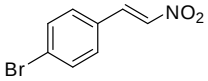
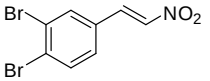
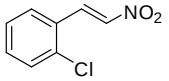
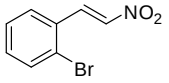
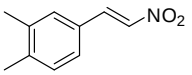
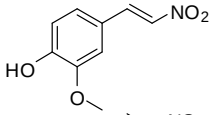
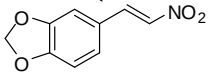
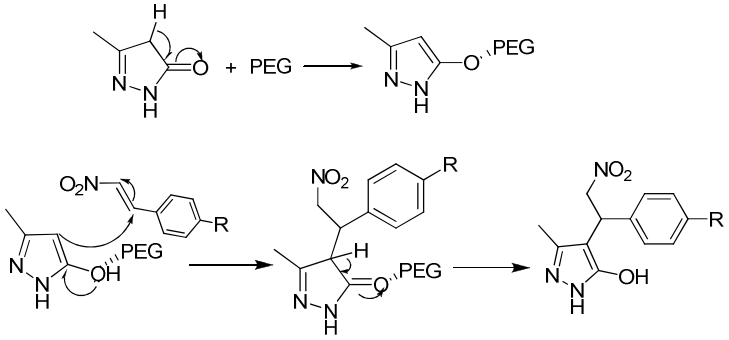


Table 1 Synthesis of 3-methyl-2-pyrazolin-5-one in presence of PEG-400

Entry	Substrate	Product	Time(h)	Yield [a] (%)
1		3a	8	85
2		3b	8	80
3		3c	10	85
4		3d	8	85
5		3e	10	85
6		3f	10	85
7		3g	10	85
8		3h	10	85
9		3i	8	90
10		3j	8	90
11		3k	12	85
12		3l	10	85
13		3m	10	90
14		3n	8	85
15		3o	12	85
16		3p	12	85

[a] *Isolated yield.*

Mechanism



A plausible reaction pathway

CONCLUSION

In conclusion, we have developed an efficient approach for the synthesis of 4-(1-aryl-2-nitroethyl)-3-methyl-1H-pyrazol-5-ol derivatives using PEG-400 without the need of any additive or acid catalyst. The mild reaction conditions, inexpensive reaction medium, operational simplicity, and high yields are the main advantages of this protocol.

REFERENCES

[1] I.K. Khanna, Y. Yu, R.M. Huff, R.M. Weier, X. Xu, F.J. Koszyk, P.W. Collins, J.N. Cogburn, P.C. Isakson, C.M. Koboldt, J.L. Masferrer, W.E. Perkins, K. Seibert, A.W. Veenhuizen, J. Yuan, D.C. Yang, Y.Y. Zhang. J. *Med. Chem*. 43, (**2000**) 3168.
[2](a) J.L. Wang, D. Liu, Z.J. Zhang, S. Shan, X. Han, S. M. Srinivasula, Croce, C.M.; Alnemri, E. S.; Huang, Z. *Proc. Natl. Acad. Sci. U.S.*A. 97 (**2000**) 7124;
(b) El-Tamany, E.S.; El-Shahed, F.A. Mohamed, B. H. *J. Serb. Chem. Soc*. 64 (**1999**) 9;
(c) M.E. A. Zaki, Soliman, H.A. Hiekal, O.A. Rashad, A.E.Z. *Naturforsch*. 61 (**2006**) 1;
(d) Z. H Ismail, G.M. Aly, M.S. El-Degwi, H.I. Heiba, M.M. Ghorab. *Egypt. J. Biotech.* 13 **2003**, 73;
(e) F.M. Abdelrazek, P. Metz, N.H. Metwally, S.F. El-Mahrouky, *Arch. Pharm.* 339, (**2006**), 456.
(f) F.M. Abdelrazek, P. Metz, O. Kataeva, A. Jaeger, S.F. El-Mahrouky. *Arch.Pharm*. 340 (**2007**) 543; (g) N. Foloppe, L.M. Fisher, R. Howes, A.G.S. Potter, Robertson, A. E. Surgenor, *Bioorg. Med. Chem*. 14 (**2006**) 4792.
[3]R. Lin, G. Chiu, Y. Yu, P.J. Connolly, S. Li, Y. Lu, M. Adams, A.R. Fuentes-Pesquera,S.L. Emanuel, L.M. Greenberger, *Bioorg. Med. Chem. Lett*. **2007**, 17, 4557.
[4]P. Pevarello, M. G. Brasca, R. Amici, P. Orsini, G. Traquandi, L. Corti, C. Piutti,P. Sansonna, M. Villa, B.S. Pierce, M. Pulici, P. Giordano, K. Martina, E.L. Fritzen,R.A. Nugent, E. Casale, A. Cameron, M. Ciomei, F. Roletto, A. Isacchi,G. Fogliatto, E. Pesenti, W. Pastori, A. Marsiglio, K.L. Leach, P.M. Clare,F. Fiorentini, M. Varasi, A. Vulpetti, M. A. Warpehoski, *J. Med. Chem.* **2004**, 47, 3367.
[5]V. Kry_stof, P. Cankar , I. Fry_sová, J. Slouka, G. Kontopidis, P.D_zubák, M. Hajdúch, J. Srovnal, W.F. de Azevedo, M. Orság, M. Paprská_rová, J. Rolík, A. Látr P.M. Fischer, M. Strnad, *J. Med. Chem*. 49 (**2006**) 6500.
[6] M.S. Squires, R.E. Feltell, N.G. Wallis, E.J. Lewis, D.M. Smith, D.M. Cross, J.F. Lyons, N.T. Thompson, Mol. *Cancer Ther*. 8 (**2009**) 324.
[7] D. Moravcová, V. Kry_stof, L. Havlícek, J. Moravec, R. Lenobel, M. Strnad, *Bioorg.Med. Chem. Lett*. 13 (**2003**) 2989.
[8] S.G. Kucukguzel, S. Rollas, H. Erdeniz, M. Kiraz, A.C. Ekinci,A. Vidin, *Eur. J. Med. Chem*. 35 (**2000**) 761.
[9]M.J. Genin, D.A. Allwine, D.J. Anderson, M.R. Barbachyn, R. Michael, D.E. Emmert, S.A. Garmon, D.R. Graber, K.C. Grega, J.B. Hester, D.K. Hutchinson, J. Morris, R.J. Reischer, J. Robert, C.W. Ford, G.E. Zurenko, E. Gray, J.C. Hamel, R.D. Schaadt, D. Ronda, D. Stapert, B.H. Yagi. *J. Med. Chem*. 43 (**2000)** 953.
[10] R. Storer, C.J. Ashton, A.D. Baxter, M.M. Hann, C.L.P. Marr, A.M. Mason, C.L. Mo, P.L. Myers, S.A. Noble, H.R. Penn, N.G. Weir, G. Niall, J.M. Woods, P.L. Coe, *Nucleosides Nucleotides* 18 (**1999**) 203.
[11]M.J. Genin, C. Biles, B.J. Keiser, S.M. Poppe, S.M. Swaney, W.G. Tarpley, Y. Yagi, D.L. Romero, *J. Med. Chem*. 43 (**2000**) 1034.
[12] G. Daidone, B. Maggio, S. Plescia, D. Raffa, C. Musiu, C. Milia,G. Perra, M.E. Marongiu, *Eur. J. Med. Chem*. 33 (**1998)** 375.

[13] S.A. Gamage, J.A. Spicer, G.W. Rewcastle, J. Milton, S. Sohal, W. Dangerfield, P. Mistry, N. Vicker, P.A. Charlton, W. A. Denny, *J. Med. Chem*. 45 (**2002**) 740.
[14] (a) G. Kamalakar, K. Komura, Y. Sugi, *Ind. Eng. Chem. Res*. 45 (**2006**) 6118;
(b) H. Weingaertner, E.U. Franck. *Angew. Chem., Int*. Ed. 44 (**2005**) 2672
[15] For recent reviews on ionic liquids, see: (a) R. Sheldon, *Chem. Commun*. **(2001**) 2399; (b) H. Zhao, S.V. Malhotra, *Aldrichim. Acta* 35 (2002)75; (c) P. Wasserstein, W. Keim,. Angew. Chem., Int. Ed. 39 (**2000)** 3772; (d) T. Welton, *Chem. Rev*. 99 *(***1999**) **2071**; (e) Y. R. Jorapur, D.Y. Chi,. *Bull. Korean Chem. Soc*. 27 (**2006)** 345.
[16] (a) P.T. Anastas, ACS Symposium Series 819: American Chemical Society,Washington, DC, 2202, p 1.; (b) P.A. Greico, Organic Synthesis in Water; Blackie Acadamic & Professional: London, 1998; (c) C.J Li, T.H. Chan, Organic Reactions in Aqueous Media; Springer: New York, NY, **1997**. pp 199; (d) N.E. Lead beater, M. Marco, Org. Lett. 4 (**2002**) 2973
[17] (a) N. Lingaiah, M. Raghu, Y. Lingappa,. *Tetrahedron Lett* 52 (**2011)** 3401; (b) N. Lingaiah, M. Raghu, Y. Lingappa, Eur. J. Chem. 1(**2010**) 228; (c) N. Lingaiah, M. Raghu, Y. Lingappa,. Synlett, (2011), 2730; (d) N. Lingaiah, M. Raghu, Y. Lingappa,. *Tetrahedron Lett*. 53 (**2012**), 1699.
[18] Meshram, H. M.; Rao, N. N.; Rao, L. C.; Kumar, N. S. *Tetrahedron Lett*. 54 (**2013**), 5941
[19] *General procedure for the synthesis of 4-(1-aryl-2-nitroethyl)-3-methyl-1H-pyrazol-5-ol in polyethylene glycol-400:* A mixture of 3-methyl-1H-pyrazol-5(4H)-one (**1**) (1 mmol) and β-nitrostyrene (**2**) (1.2 mmol) was suspended in 5mL of PEG-400. The reaction mixture was heated at 60 ^{O}C and the progress of the reaction was monitored by TLC. After completion of the reaction, the solid product obtained was filtered, and washed with water (2 ×10 mL) and n-hexane (3×10 mL). Then the solid was dried under vacuum to obtain the crude product which was purified (**3**) by column chromatography using EA/hexane as eluent to afford the pure product.