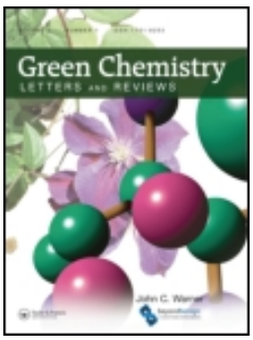

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ORIGINAL ARTICLE

Synthesis of 3-amino 1*H*-pyrazoles catalyzed by *p*-toluene sulphonic acid using polyethylene glycol-400 as an efficient and recyclable reaction medium

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An efficient synthesis of 3-amino 1*H*-pyrazoles is described. The reaction of β-keto nitriles with hydrazines in the presence of a catalytic amount of *p*-toluene sulphonic acid using polyethylene glycol-400 as an efficient and recyclable reaction medium afforded the corresponding 3-amino 1*H* pyrazoles excellent yields.

Keywords: Polyethylene glycol-400; *p*-toluene sulphonic acid; β-keto nitriles; hydrazines; 3-amino 1*H*-pyrazoles

Introduction

Pyrazoles, in particular 3-amino 1*H*-pyrazoles, are an important class of compounds in medicinal chemistry, possessing a large number of pharmacological properties, such as being anti-hypertensive (*1*), anti-bacterial (*2*), anti-inflammatory, muscle relaxants (*3*,*4*) and acting as inhibitors of cyclin-dependent kinases (CDK), such as CDK_2/cycling A–E (*5*). They are also potent and selective aurora kinase inhibitors (*6*,*7*). In addition, 3-amino 1*H*-pyrazoles have an industrial application in the inhibition of corrosion on metals, such as Zn, Cu, Al and brass (*8*). Despite their importance from pharmacological, industrial and synthetic points of view, comparatively few methods for the preparation of 3-amino 1*H*-pyrazoles have been reported. These include condensation of hydrazines with β-keto nitriles (*9*), β-formyl nitriles (*4*), β-methoxy vinyl nitriles (*10*), α-nitrilo ethyl acetate (*11*), and solid supported condensation of β-keto nitriles (*12*). However, reported procedures involve one or more limitations, such as incomplete conversion of the starting materials, long reaction times, and tedious work-up procedures with unsatisfactory yields. Thus, an efficient and general method for the synthesis of 3-amino 1*H*-pyrazoles is highly desirable.

In recent years, polyethylene glycol promoted reactions (*13*) have attracted the attention of organic chemists due to their solvating ability and aptitude to act as a phase transfer catalyst, negligible vapor pressure, easy recyclability, reusability, ease of work-up, eco-friendly nature, and economical cost. Additionally, *p*-toluene sulphonic acid is cheap, commercially available in its anhydrous forms, and is used in various organic transformations (*14*). In this context, we report here an efficient and facile method for the synthesis of 3-amino 1*H*-pyrazoles by the condensation of β-keto nitriles and hydrazines in the presence of *p*-toluene sulphonic acid using polyethylene glycol as an efficient and recyclable reaction medium.

Results and discussion

In this report (Scheme 1), we describe an efficient and facile method for the synthesis of 3-amino 1*H*-pyrazoles in the presence of *p*-toluene sulphonic acid using PEG-400 as an efficient and reusable reaction medium. This method does not require expensive reagents or special care to exclude the moisture from the reaction medium. We first examined the reaction of benzoyl acetonitrile, i.e. β-keto nitrile (*15*) with 4-hydrazinobenzoic acid in PEG-400 using *p*-toluene sulphonic acid (0.01 equiv.) as a catalyst at 80°C to yield the corresponding 3-amino 1*H*-pyrazoles in 98%. In order to optimize the reaction conditions, we carried out the above reaction in different solvents, such as acetonitrile, ethanol, dichloromethane, isopropyl alcohol, benzene and PEG-400, using 0.01 equiv. of *p*-TSA. We found the PEG-400 an efficient reaction medium in terms of reaction time as well as yield (98%) (Table 1). Furthermore, increasing the amount of *p*-TSA from 0.01 to 1.0 equiv. had no effect on the rate of the reaction or the yield of the product, and we believe that the *p*-toluene

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Table 1. Solvent effect on the reaction of benzoyl acetonitrile and 4-hydrazino benzoic acid catalyzed by *p*-toluene sulphonic acid.

Entry	Solvent (°C)	*p*-TSA (equiv.)	Time	Yield (%)
1	CH3CN (80)	0.01	1	90
2	EtOH (80)	0.01	1	92
3	DCM (40)	0.01	2	60
4	C6H6 (80)	0.01	2	50
5	IPA (80)	0.01	2	92
6	PEG-40 (80)	0.01	1	98
7	PEG-400 (80)	0.1	1	99
8	PEG-400 (80)	0.5	1	98
9	PEG-400 (80)	1	1	98

Table 2. Synthesis of 3-amino 1*H*-pyrazoles catalyzed by *p*-toluene sulphonic acid using PEG-400 as an efficient reaction medium.

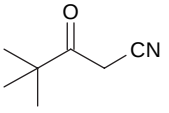
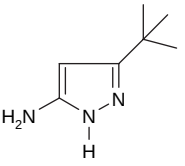
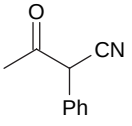
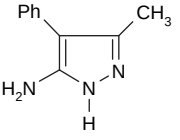
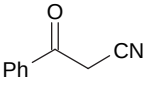
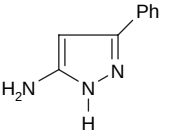
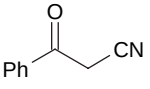
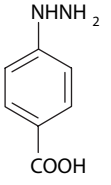
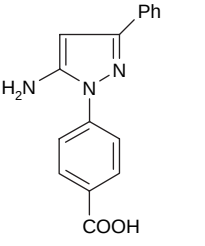
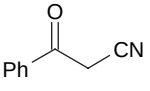
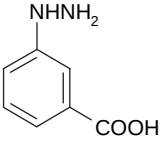
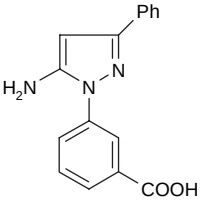
Entry	β-Keto nitrile	Hydrazine	Product[a]	Time (h)	Yield (%)
3a		$NH_2NH_2H_2O$		1	98
3b		$NH_2NH_2H_2O$		1.5	98
3c		$NH_2NH_2H_2O$		1	98
3d				1	99
3e				3	93

Table 2 (*Continued*)

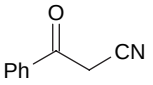
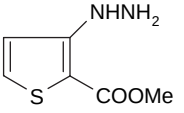
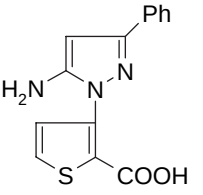
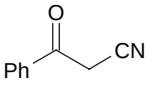
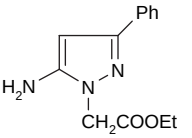
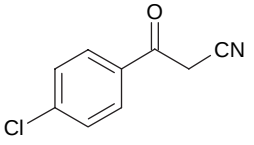
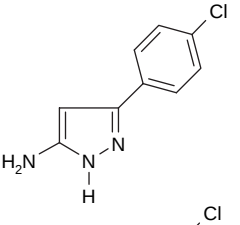
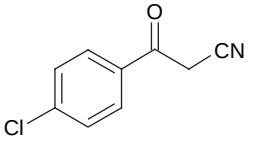
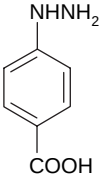
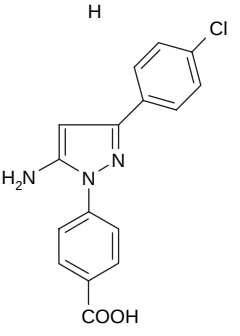
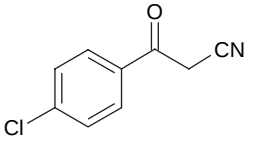
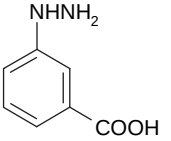
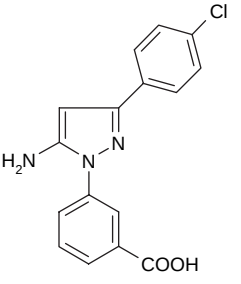
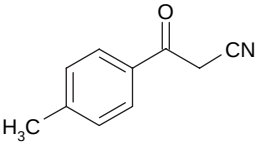
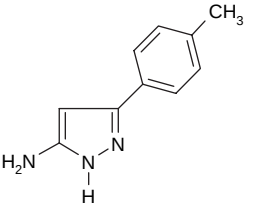
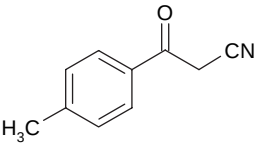
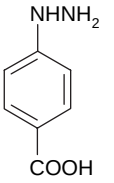
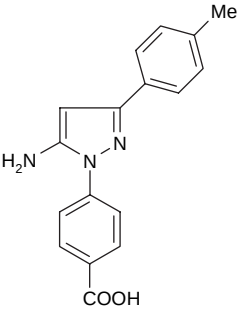
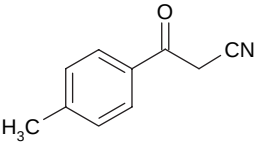
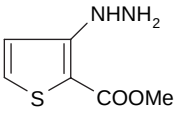
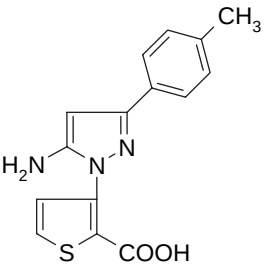
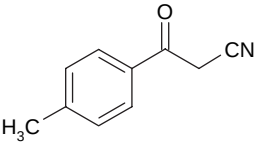
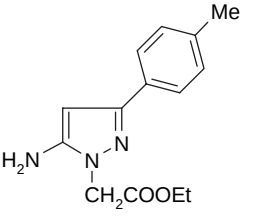
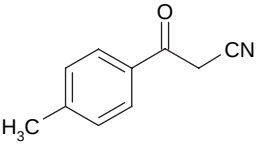
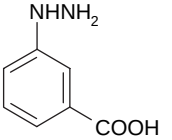
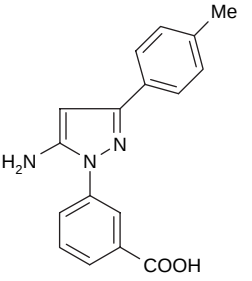
Entry	β-Keto nitrile	Hydrazine	Product[a]	Time (h)	Yield (%)
3f				1	99
3g		NH_2NHCH_2COOEt		2.5	98
3h		$NH_2NH_2H_2O$		1	96
3i				1	99
3j				3	94
3k		$NH_2NH_2H_2O$		1	98

Table 2 (*Continued*)

Entry	β-Keto nitrile	Hydrazine	Product[a]	Time (h)	Yield (%)
3l				1	97
3m				1	99
3n		NH_2NHCH_2COOEt		2	98
3o				3	96

[a]Isolated yields after column chromatography and all products gave satisfactory spectral (^{1}HNMR, EIMS) data.

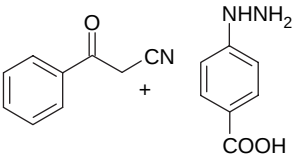
sulphonic acid facilitates the reaction by donating the proton throughout the reaction (Scheme 3). This result encouraged us to carry out the reaction on several β-keto nitriles with different hydrazines in the presence of *p*-toluene sulphonic acid (0.01 equiv.) in PEG-400 to afford the corresponding products excellent yields (Table 2). In addition, it is noticed that the PEG-400 was recovered and reused for six runs without loss of its activity (Table 3). From the forgoing results, it is evident that the *p*-toluene sulphonic acid is an excellent catalyst for the synthesis of 3-amino 1*H*-pyrazoles and PEG-400 as an efficient and recyclable reaction medium.

Experimental section

Typical experimental procedure

A stirred solution of β-keto nitrile (1 mmol), hydrazine (1 mmol) in polyethylene glycol-400 (10 ml), was

Table 3. Synthesis of 3-amino 1*H*-pyrazoles using *p*-toluene sulphonic acid (0.01 equiv.) in PEG-400 as an efficient and reusable reaction medium.

Entry	Substrates	Time (h)	Yield (%)
1		1	98
2	2nd run	1	97
3	3rd run	1	98
4	4th run	1	98
5	5th run	1	97
6	6th run	1	97

added to *p*-TSA (0.01 mmol) and stirred at 80°C for an appropriate time (Table 1). On completion of the reaction, as monitored by TLC, the product was extracted into ethyl acetate (3 × 20 ml). The combined organic layer was washed with saturated sodium bicarbonate followed by brine solution, then dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to afford crude product and purified by silica gel column chromatography. The polyethylene glycol (PEG)-400 was recovered and reused without loss of activity. Spectral data for selective compounds Table I, **3d**: IR (KBr): 3414, 1616, 1091 cm^{-1}; ^1H NMR (200 MHz, DMSO + $CDCl_3$): δ 6.60 (s, 1H), 7.40 (m, 5H), 7.8 (d, 2H, $J = 8.50$), 8.40 (d, 2H, $J = 8.50$); EIMS: *m*/*z* 279. **3e**: IR (KBr): 3414, 1617, 1383, 618 cm^{-1}; ^1H NMR (200 MHz, DMSO + $CDCl_3$): δ 5.9 (s, 1H), 7.15 (m, 5H), 7.35 (d, 1H, $J = 8.15$), 7.60 (t, 1H, $J = 3.15$), 7.85 (d, 1H, $J = 8.25$), 7.9 (d, 1H, $J = 8.15$), 8.30 (s, 1H); EIMS: *m*/*z* 279. **3f**: IR (KBr): 3415, 1618, 1285, 761 cm^{-1}; ^1H NMR (200 MHz, DMSO + $CDCl_3$): δ 3.90 (s, 3H), 6.25 (s, 1H), 7.40 (m, 5H), 7.7 (d, 2H, $J = 8.25$), 8.05 (d, 2H, $J = 8.25$); EIMS: *m*/*z* 287. **3l**: IR (KBr): 3415, 1617, 1384, 764, 619 cm^{-1}; ^1H NMR (200 MHz, DMSO + $CDCl_3$): δ 2.37 (s, 3H), 3.75 (b s, 2H), 7.1 (d, 2H, $J = 8.22$), 7.4 (d, 2H, $J = 8.15$), 7.7 (d, 2H, $J = 8.15$), 8.0 (d, 2H, $J = 8.22$); EIMS: *m*/*z* 291. **3m**: IR (KBr): 3415, 1618, 1384, 1216, 1047, 816, 619, 476 cm^{-1}; ^1H NMR (200 MHz, DMSO + $CDCl_3$) δ 2.1 (t, 3H) 2.35 (s, 3H), 3.9 (q, 2H) 6.25 (s, 1H), 7.1 (d, 2H, $J = 8.25$), 7.6 (d, 2H, $J = 8.25$), 7.7 (d, 2H, $J = 8.15$), 8.1 (d, 2H, $J = 8.15$); EIMS: *m*/*z* 299, 301.

Conclusion

In conclusion, we have described the efficient synthesis of 3-amino 1*H*-pyrazoles by the condensation of β-keto nitriles and hydrazines in the presence of a catalytic amount of *p*-toluene sulphonic acid in PEG-400. The present procedure has the advantage of less reaction time, improved yields of the products, and recyclability of the reaction medium, thus making it a useful and important addition to the existing methods.

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References

(1) Almansa, C.; Gomez, L.A.; Cavalcanti, F.L.; Arribade, A.F.; Garcia, J.-R.; Form, J. *J. Med. Chem.* **1997**, *40*, 547.

(2) a) Daidone, G.; Maggio, B.; Plescia, S.; Raffa, D.; Musiu, C.; Milia, C.; Perra, G.; Marongiu, M.E. *Eur. J. Med. Chem.* **1998**, *33*, 375; b) Finn, J.; Mattia, K.; Morytko, M.; Ram, S.; Yang, Y.; Wu, X.; Mak, E.; Gallant, P.; Keith, D. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2231.

(3) a) Penning, T.D.; Talley, J.J.; Bertenshaw, S.R.; Carter, J.S.; Collins, P.R.; Docter, S.; Graneto, M.J.; Lee, L.F.; Malecha, J.W.; Miyashiro, J.M. et al. *J. Med. Chem.* **1997**, *40*, 1347; b) Zhihua, S.; Guan, J.; Michael, F.P.; Kathy, M.; Michael, W.P.; William, M.V.; Monica, S.; Michele, S.; Dave, R.M.; Dennis, C. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 601.

(4) Elvin, L.A.; John, E.C.; Leon, C.G.; John, J.L.; Harry, E.R. *J. Med. Chem.* **1964**, *7*, 259.

(5) Pevarello, P.; Brasca, M.G.; Orsini, P.; Traquandi, G.; Longo, A.; Nesi, M.; Orzi, F.; Piutti, C.; Sansonna, P.; Varassi, M. et al. *J. Med. Chem.* **2005**, *48*, 2944.

(6) Fancelli, D.; Berta, D.; Bindi, S.; Cameron, A.; Cappella, P.; Carpinelli, P.; Catana, C.; Forte, B.; Giordano, P.; Giorgini, M.L. et al. *J. Med. Chem.* **2005**, *48*, 3080.

(7) Dymek, W.; Janik, B.S.; Ryznerski, Z. *Acta. Polon. Pharma*. **1966**, *23*, 207.
(8) a) Allah, A.G.; Hefny, M.M.; Salih, S.A.; Basouny-El, M.S. *Corrosion*. **1989**, *45*, 574; b) Allah, A.G.; Badawy, M.W.; Reham, H.H.; Abou-Romia, M.M. *J. Appn. Electro Chem*. **1989**, *19*, 928; c) Badawy, W.A.; Hefny, M.M.; Egany-El, S.S. *Corrosion*. **1990**, *46*, 978; d) Abou-Romia, M.M.; Abd Rahaman-El, H.A.; Sayed-El, H.A.M. *Bull. Electrochem*. **1990**, *6*, 757.
(9) a) Latha, D.; Srinivasa Rao, K. *Org. Prep. Proced*. **2004**, *36*, 494; b) Jagath Reddy, G.; Latha, D.; Srinivasa Rao, K. *Cheminfom*. **2005**, *36*, 120; c) Joshi, K.C.; Pathak, V.N.; Garg, U. *J. Het. Chem*. **1979**, *16*, 1141.
(10) Hanefeld, U.; Rees, C.W.; White, A.J.P. *J. Chem. Soc. Perkin Trance-I*, **1996** *1545*.
(11) Vanotti, E.; Fiorentini, F.; Villa, M. *J. Het. Chem*. **1994**, *31*, 737.
(12) Dodd, D.S.; Martinez, R.L.; Kamau, M.; Ruam, Z.; Kirk, K.V.; Cooper, C.B.; Hermsmeier, M.A.; Traeger, S.C.; Poss, M.A. *J. Comb. Chem*. **2005**, *7*, 584.
(13) a) Suryakiran, N.; Srikanth Reddy, T.; Asa Latha, K.; Lakshman, M.; Vemkateswarlu, Y. *Tetrahedron Lett*. **2006**, *47*, 3853; b) Dickerson, T.J.; Reed, N.N.; Janda, K.D. *Chem. Rev*. **2002**, *102*, 3325; c) Kamal, A.; Reddy, D.R.; Rajender. *Tetrahedron Lett*. **2005**, *46*, 7951.
(14) a) Khospour, A.R.; Kodhoaei, M.M.; Monghannian, H. *Synlett*. **2005**, 955; b) Khospour, A.R.; Esmaeilpoor, K.; Moradie, A. *J. Iran. Chem. Soc*. **2006**, *3*, 81. c) Shanmugam, G.; Madhavi, M.; Anil Kumar, P.; Prabhakahr, M.; Venu, N.; Venkataraman, S.; Vijayavitthal, T.M.; Mahesh Reddy, G.; Ravindra Kumar, Y. *Chemlform*. **2005**, *36*, 46.
(15) a) Dorsch, J.B.; Mcelvain, S.M. *J. Amer. Chem. Soc*. **1932**, *54*, 2960; b) Wang, G.; Liu, X.; Zhao. G. *Tetrahedron*: *Asymmetry*. **2005**, *16*, 1873.