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Microwave assisted synthesis of 3-amino 1H-pyrazoles catalyzed by p-toluenesulphonic acid

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ABSTRACT

An efficient synthesis of 3-amino 1H-pyrazoles is described. Reaction of β-keto-nitriles with hydrazines in the presence of catalytic amount of p-toluenesulphonic acid under microwave irradiation afforded the corresponding 3-amino 1H-pyrazole in excellent yields. The method is general for the preparation of a wide variety of 3-amino 1H-pyrazole.

KEYWORDS

Microwave irradiation p-Toluenesulphonic acid;
β-keto-nitriles;
Hydrazines;
3-amino 1H-pyrazoles.

INTRODUCTION

Pyrazole nucleus is an important pharmacophore in medicinal chemistry. Among pyrazoles, the 3-amino 1H-pyrazoles are very significant class of compounds as they posses large no of pharmacological properties such as, anti-hypertensive[1], anti-bacterial[2], anti-inflammatory and muscle relaxant[3-4], and inhibitor of cyclin dependent kinases(CDK) like CDK_2/cycling A-E as new anti-tumor agents[5]. They are also potent and selective aurora kinase inhibitors[6-7]. In addition the 3-amino 1H-pyrazoles also have industrial appliance in inhibition of corrosion on metals like Zn, Cu, Al and Brass[8]. This has led to development of new synthetic methodologies. In general the 3-amino 1H-pyrazole are obtained by the condensation of hydrazines with β-keto-nitriles[9], β-formyl nitriles[4], β-methoxy vinyl nitriles[10], α-nitrilo ethyl acetate and a solid supported condensation of aryl hydrazine with β-keto-nitriles[11]. However, most of them suffers from one or other limitations such as incomple tion of starting materials even on prolonged reaction time, unavailability of the reagents, tedious workup procedures with unsatisfactory yields. Thus an efficient and general procedure for the synthesis of 3-amino 1H-pyrazole is highly desirable.

The driving force for microwave developments in organic synthesis[12-19] have many facts. The organic reactions assisted by microwaves in particular have been gained special attention, because the use of microwave activation in organic synthesis can increase the purity of the resulting products and shorten the reaction time. The increasing requirement for environmentally clean technology that minimizes the production of waste at source, microwave may offer cleaner reactions by improving product yields and selectivities, enhancing the product recovery. Herein we report an efficient synthesis of 3-amino 1H-pyrazoles under microwave irradiation using p-toluenesulphonic acid as a catalyst.

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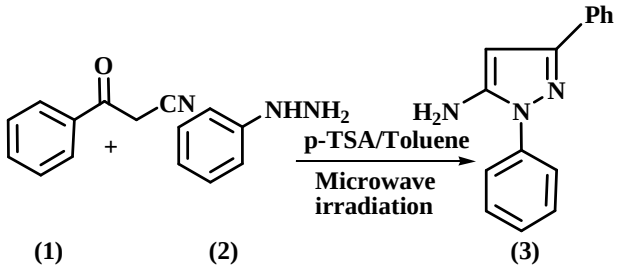


TABLE 1 : Optimization of reaction conditions on reaction of benzoylacetonitrile with p-hydrazino benzoic acid using different catalysts under microwave irradiation conditions

Entry	Catalyst (equiv.)	Time(min)	Yield(%)
1	$FeCl_3$ (0.5)	5	30
2	$Bi(OTf)_3$ (0.5)	5	50
3	$ZrCl_4$ (0.5)	5	70
4	$La(NO_3)_3.6H_2O$ (0.5)	5	30
5	p-TSA (0.5)	5	95
6	p-TSA (0.4)	3	95
7	p-TSA (0.3)	3	95
8	p-TSA (0.1)	3	95

RESULTS AND DISCUSSION

In this report (SCHEME 1), we have described an efficient and general procedure for the synthesis of 3-amino 1H-pyrazole. The present method do not involve tedious reaction conditions, on simple microwave irradiation in the presence of catalytic amount of p-toluenesulphonic acid gives the corresponding 3-amino 1H-pyrazole in excellent yields. And the obtained products were completely free from starting materials which are left remain in conventional method as impurities. The p-toluenesulphonic acid was removed by simple washing of 5% ethyl acetate in hexane and on filtration to gave the desired product in >95% HPLC purity. Initially, we carried out the reaction of benzoylacetonitrile i.e. -keto-nitriles[20-21] with p-hydrazino benzoic acid and p-toluenesulphonic acid as a catalyst under microwave irradiation to yield the corresponding 3-amino 1H-pyrazole in 95%. This success has encouraged us to carry out the reaction in the presence of p-toluenesulphonic acid as a catalyst under microwave irradiation. In order to optimize the reaction conditions we carried out the above reaction in the presence of different catalysts such as $FeCl_3$, $Bi(OTf)_3$, $ZrCl_4$, $La(NO_3)_3.6H_2O$ and p-TSA. We found that p-toluenesulphonic acid is to be most effective catalyst in terms of reaction time as well as yield(>95) for the synthesis of 3-amino 1H-pyrazoles, whereas other catalysts formed the products with varying yields 30-70%. The experimental procedure for this reaction is remarkably simple and no dry conditions are required. Further we carried out the reaction in conventional method under refluxing temperature for 16h, which also gave the corresponding 3-amino 1H-pyrazole. Under above conditions, in many cases it is noticed that in the absence of p-toluenesulphonic acid, the reaction is incomplete and uncyclized product was isolated along with 3-amino 1H-pyrazole.

EXPERIMENTAL

Typical experimental procedure (Microwave)

A mixture of β-keto-nitile(10mmol), hydrazine (10mmol), p-TSA(0.1mmol) and toluene(5 mL) were mixed in a test tube, and the mixture was irradiated in laboratory microwave(Ethos 1600, 650W) at 100^0C for appropriate minutes. After complete conversion, as monitored by TLC, the solvent was evaporated, added 5% ethyl acetate in hexane(10mL) and stirred for 10min for washing, filtered to give corresponding pure 3-amino 1H-pyrazoles in excellent yields.

Typical experimental procedure(Conventional)

A solution of β-keto-nitrile(10mmol), hydrazine (10mmol), p-TSA(0.1mmol) in toluene(5mL), was stirred at refluxing temperature for 1-6 h. After completion of the reaction, as monitored by TLC, the solvent was evaporated, added 5% ethyl acetate in hexane (10mL), and stirred for 10min for washing, and filtered to give corresponding pure 3-amino 1H-pyrazoles.

3-amino 4-phenyl 5-methyl 1H-pyrazole(Entry 1)

IR(KBr): 3420, 1620, 1520, 750cm^{-1}. ^{1}H NMR(200 MHz, DMSO+$CDCl_3$): δ=2.26(s, 3H), 4.75(s, 2H br), 7.40(s, 5H). EIMS: m/z, 173.

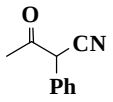
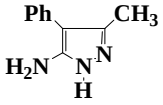
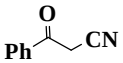
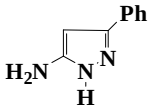
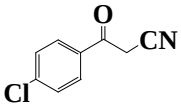
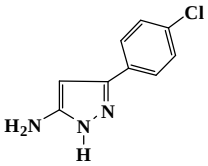
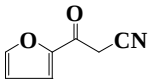
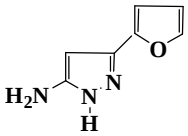
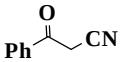
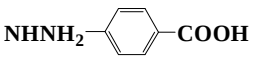
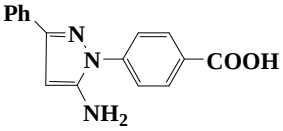
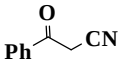
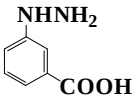
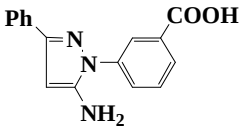
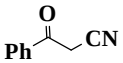
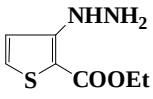
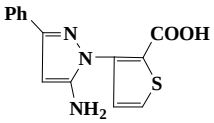
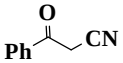
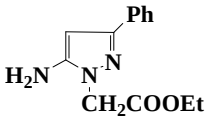
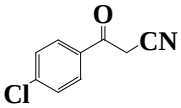
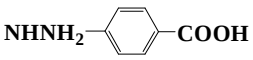
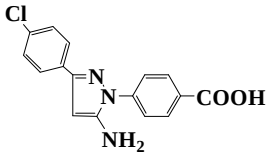
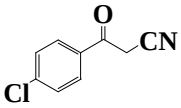
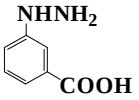
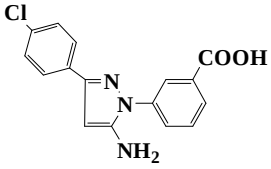
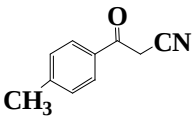
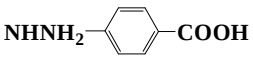
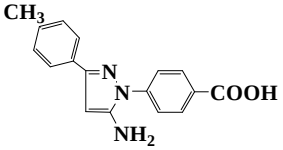
3-amino 5-phenyl 1H-pyrazole(Entry 2)

IR(KBr): 3415, 1618, 1124, 613cm^{-1}. ^{1}H NMR(200 MHz, DMSO+$CDCl_3$) δ=4.25(b s, 2H), 5.75(s, 1H), 7.30(m, 5H). EIMS: m/z, 157.

3-amino 5-(tolyl) 1H-pyrazole(Entry 3)

IR(neat): 3448, 1636cm^{-1}. ^{1}H NMR(200MHz, DMSO +$CDCl_3$): δ=2.65(s, 3H), 5.5(s, 1H), 7.25(d, 2H), 7.35 (d, 2H). EIMS: m/z, 191, 193, relative intensity 1:3.

TABLE 2 : Synthesis of 3-amino 2H-pyrazole catalyzed by p-toluenesulphonic acid under solvent and solvent free conditions

Entry	β-Keto-nitrile	Hydrazine	Product	Time (min)	Yield (%)
1		$NH_2NH_2H_2O$		3	90
2		$NH_2NH_2H_2O$		3	92
3		$NH_2NH_2H_2O$		3	95
4		$NH_2NH_2H_2O$		3	95
5				3	93
6				5	93
7				3	95
8		NH_2NHCH_2COOEt		5	95
9				3	95
10				5	92
11				3	95

[a]Isolated yields after column chromatography/crystallization and all products gave satisfactory spectral and analytical data

3-amino5-(2-furyl) 1H-pyrazole(Entry 4)

IR(KBr): 3415, 1694, 1615, 1179, 616cm^{-1}. ^{1}H NMR (200MHz, DMSO+$CDCl_3$): δ=5.68(s, 1H), 6.41(s, 1H), 6.59(s, 1H), 7.4(s, 1H). EIMS: m/z, 149.

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3-amino 5-phenyl 1-(4-benzoic acid) 1H-pyazole (Entry 5)

IR (KBr): 3414, 1616, 1091cm^{-1}. ^{1}H NMR(200MHz, DMSO+$CDCl_3$):δ=6.60(s, 1H), 7.40(m, 5H), 7.8(d, 2H), 8.40(d, 2H). EIMS: m/z, 279.

3-amino 5-phenyl 1-(3-benzoic acid) 1H-pyrazole(Entry 6)

IR(KBr): 3414, 1617, 1383, 618cm^{-1}. ^{1}H NMR(200 MHz, DMSI+$CDCl_3$): δ=5.9(s, 1H), 7.15(m, 5H), 7.35(d, 1H), 7.60(t, 1H), 7.85(d, 1H), 7.9(d, 1H), 8.30(s, 1H). EIMS: m/z, 279.

.3-amino 5-phenyl 1-(3-thiophene 2-methyl carboxylate) 1H-pyrazole(Entry 7)

IR(KBr): 3415, 1618, 1285, 761cm^{-1}. ^{1}H NMR(200 MHz, DMSO+$CDCl_3$):δ=3.90(s, 3H), 6.25(s, 1H), 7.40(m, 5H), 7.7(d, 2H), 8.05(d, 2H). EIMS: m/z, 287.

3-amino 5-phenyl 1-(ethyl acetate) 1H-pyrazole (Entry 8)

IR (KBr): 3415, 1657, 1615, 1384, 1121, 758cm^{-1}. ^{1}H NMR(200MHz, DMSO+$CDCl_3$): δ=1.25(t, 3H), 4.25(q, 2H), 4.925(s, 2H), 5.85(s, 1H), 7.5(m, 5H). EIMS: m/z, 245.

3-amino(5-(4-chloro phenyl) 1-(4-benzoic acid)) 1H-pyrazole(Entry 9)

IR(KBr): 3416, 1650, 1384, 1120, 758cm^{-1}.^{1}H NMR (200MHz, DMSO+$CDCl_3$) δ=6.02(s, 1H), 7.15(d, 2H), 7.35(d, 2H), 7.60(d, 2H), 8.10(d, 2H). EIMS: m/z, 303, 305, relative intensity 1:3.

3-amino(5-(4-chloro phenyl) 1-(3-benzoic acid)) 1H-pyrazole(Entry 10)

IR(KBr): 3415, 1650, 1090cm^{-1}.^{1}H NMR(200MHz, DMSO+$CDCl_3$) δ=6.8(s, 1H), 7.4(d, 2H), 7.6(t, 1H), 7.8(d, 3H), 8.1(d, 1H), 8.3(s, 1H), 9.93(s, 1H). EIMS: m/z, 303, 305, relative intensity 1:3.

3-amino(5-(4-tolyl) 1-(4-benzoic acid)) 1H-pyrazole(Entry 11)

IR(KBr): 3415, 1617, 1384, 764, 619cm^{-1}. ^{1}H NMR (200MHz, DMSO+CDCl3) δ=2.37(s, 3H), 3.75(s, 2H broad), 7.1(d, 2H), 7.4(d, 2H), 7.7(d, 2H), 8.0(d, 2H). EIMS: m/z, 291.

CONCLUSION

In Conclusion, we have described a novel and highly efficient methods for the synthesis of 3-amino1H-pyrazole. The present procedure has the advantage of high efficient reduced reaction time with high yields of products and simple work-up procedure, which makes it is a useful and important addition to the present existing methods.

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REFERENCES

[1] C.Almansa, L.A.Gomez, F.L.Cavalcanti, A.F. Arriba, J.D.Rafanell, J.G.Form; J.Med.Chem., **40**, 547 **(1997)**.

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

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

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

[5] P.Pevarello, M.G.Brasca, P.Orsini, G.Traquandi, A.Longo, M.Nesi, F.Orzi, C.Piutti, P.Sansonna, M. Varassi, A.Cameron, A.Vulpetti, F.Roletto, R.Alzani, M.Ciomei, C.Alanese, W.Pastori, A.Marsiglio, E. Pesenti, F.Fiorentini, R.Bischoff, C.Mercurio; J. Med.Chem., **48**, 2944 **(2005)**.

[6] D.Fancelli, D.Berta, S.Bindi, A.Cameron, P. Cappella, P.Carpinelli, C.Catana, B.Forte, P.Giordano,

M.L.Giorgini, S.Mantegani, A.Marsiglio, M.Meroni, J.Moll, V.Pittala, F.Roletto, D.Severino, C.Soncini, P.Storici, R.Tonani, M.Varasi, A.Vulpetti, P.Vianello; J.Med.Chem., **48**, 3080 **(2005)**.

[7] W.Dymek, B.S.Janik, Z.Ryznerski; Acta, Polon. Pharm., **23**, 207 **(1966)**.

[8] **(a)** A.G.Allah, M.M.Hefny, S.A.Salih, M.S.El-Basouny; Corrosion, **45**, 574 **(1989)**.
(b) A.G.Allah, M.W.Badawy, H.H.Reham, M.M. Abou-Romia; J.Appl.Electrochem., **19**, 928 **(1989)**.
(c) W.A.Badawy, M.M.Hefny, S.S.El-Egany; Corrosion, **46**, 978 **(1990)**.
(d) M.M.Abou-Romia, H.A.Abd El-Rahaman, H. A.M.El-Sayed; Bull.Electrochem., **6**, 757 **(1990)**.

[9] K.C.Joshi, V.N.Pathak, U.Garg; J.Heterocycl. Chem., **16**, 1141 **(1979)**.

[10] U.Hanefeld, C.W.Rees, A.J.P.White; J.Chem.Soc., Perkin Trans. 1, 1545 **(1996)**.

[11] **(a)** D.S.Dodd, R.L.Martinez, M.Kamau, Z.Ruam, K.V.Kirk, C.B.Cooper, M.A.Hermsmeier, S.C. Traeger, M.A.Poss; J.Comb.Chem., **7**, 584 **(2005)**.
(b) D.Villemin; A.Benalloum, Synth.Commun., **21**, 1 **(1991)**.

[12] A.Lupy; Topics in Current Chem., **206**, 153 **(1999)**

[13] D.Villemin, B.Labiad, A.Loupy;Synth.Commun., **23**, 419 **(1993)**.

[14] M.Larhed, A.Halberg; J.Org.Chem., **51**, 9582 **(1996)**.

[15] C.D.Wang, S.Xin-Zhong, R.J.Xie; Synth.Commun., **27**, 2517 **(1997)**.

[16] R.S.Varma, R.Dahiya; Tetrahedron Lett., **38**, 2034 **(1997)**.

[17] M.Hosseini Sarvari, H.Sharghi; J.Org.Chem., **69**, 6953 **(1997)**.

[18] A.I.Bosch, P.Cruz, E.Eiez-Barra, A.Loupy, F.Langa; Synlett, 1259 **(1995)**.

[19] A.R.Khosropour, M.M.Khodaei, H.Moghannian; Synlett, 955 **(2005)**.

[20] J.B.Dorsch, S.M.Mcelvain; J.Am.Chem.Soc., **54**, 2960 **(1932)**.

[21] G.Wang, X.Liu, G.Zhao; Tetrahedron Asymmetry, **16**, 1873 **(2005)**.