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An enviornmentally benign one-pot synthesis of 3-aryl-furo[3,2-c]coumarins in PEG-400 and water

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ABSTRACT

A Facile, ecofriendly, one-pot protocol for the synthesis of substituted 3-phenyl-furo[3,2-c]coumarins from in-situ generated α-halo ketones and 4-hydroxy coumarins in PEG-400 and water as a greener solvent. The developed protocol provides the better alternative to the existing method as it involves utilization of in-situ generated α-halo ketones and avoids the use of lachrymatric α-haloketones as well as toxic organic solvents.

Keywords PEG-400, One-pot, N-bromosuccinimide, 3-phenyl-furo[3,2-c]coumarins, Acetophenones

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INTRODUCTION

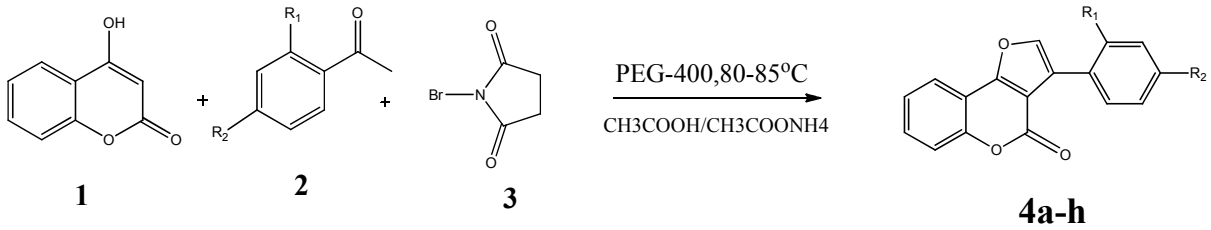
Multicomponent one pot synthesis has gaining popularity primarily concerned with environmentally benign synthesis due to features of atom economy and preparation of various organic molecules by the introduction of several diverse elements.[1] Furocoumarin derivatives are naturally occurring compounds and exhibit various biological activities such as antitumor, HIV inhibitory, anti-influenza, anti-inflamatory ,antitumor, anticoagulant, antimicrobial ,insectisidal , antioxidant these facts prompted us to design and develop new synthetic protocol for the synthesis of them[2-10].Although previous studies provided much information about the biological activities, but several questions remains unanswered.

Recently many improved methods designed to synthesis of furo[3,2-C]coumarins using piperidine /toluene).[11] using α-tosyloxyketones.[12] In this approach instead of using toxic, corrosive and irritating bromine we used user friendly N-bromosuccinimide for the selective mono- bromination of various substituted acetophenones and avoid the use of lachrymatric ,toxic and comparatively less stable α-halo ketones. PEG is non-toxic ,easily available, inexpensive, non-ionic liquid medium of low volatility, thermally stable, reusable, also are phase transfer catalyst.[13] Many organic reaction carried out under PEG-400 are gaining popularity like Heck reaction, Baylis-Hillman, Bignelli , Wacker etc. Ionic liquid solvents are also the most popular solvent but are very expensive than that of PEG.[14] Their toxicity and environmental effects are the most part unknown .[15]

Only few methods have been describe for the synthesis of substituted furo[3,2-c]coumarins; Zinab Zareai and co-workers reported synthesis of furo[3,2-c]coumarins via one –pot oxidative pseudo three component reaction .We have developed a versatile, environmentally benign convenient protocol for the synthesis of differently substituted 3-phenyl-furo[3,2-c]coumarins from cyclocondesation of in-situ generated α-bromo ketones and 4- hydroxy coumarins in PEG-400 as a greener medium to obtained high yield . In order to generate α-bromo ketones in situ we

have carried out bromination of substituted acetophenones with N-bromo succinimide in PEG-400 at 85^{0c}. Main advantaged of this protocol is no need to isolate in situ generated lachrymatric α-bromo ketones and yield relatively high.

Scheme:1



SYNTHESIS OF 3-PHENYL-FURO[3,2-C]COUMARINS

MATERIALS AND METHODS

Acetophenones , NBS and 4-Hydroxy coumarin used in this work were used without further purification .melting points were taken in open capillary and are un-corrected. IR spectra were recorded using KBr (disc)on the JASCOFT-IR 4100,Japan,1H NMR AND 13C NMR Spectra recorded on 300 mhz spectrometer. silica gel from Aldrich .inc. was used for column chromatography. Chemical shifts are reported in parts per million as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet).

General procedure for synthesis of 4(a-j)

A mix. of aromatic acetophenone (5 mmol), NBS(5.5 mmol) in PEG-400 and water 1:2 proportion was stirred for 30 min at 85^{o}C . The formation of α-Bromoketone was monitored by thin layer chromatography (TLC).After completion of bromination, add the solution of 4-hydroxy coumarin (5mmol) and acetic acid and ammonium acetate(4:1) in PEG-400 and reaction mass further stirred for 30 min. The progress of reaction was monitored by Thin layer chromatography (TLC) .After completion of reaction 25 ml of ethyl acetate were added and stirred for 20 min. this process repeated twice. The combined Ethyl acetate phase was removed under reduced pressure and resulting crude product was purified by flash chromatography (20% Ethyl acetate/Pet ether) to give corresponding 3-Aryl-furo[3,2-c]coumarins (**4a-h**) and mother liquor kept aside for further runs .

RESULT AND DISCUSSION

To determine the fate of proposal, we have carried out simple reaction of Acetophenone, NBS in water and stirred for 30min.at 85^{o}C but it was observed that without use of PEG-400 reaction dose not proceed. when we used PEG-400 a catalytic amount and water as a solvent followed by addition of solution of 4-Hydroxy coumarins in $ACOH/ACONH_4$(4:1) yielded cycloadduct 3-phenyl-furo[3,2-C]coumarins in good yield **table1**. All the compounds characterized by IR, ^{1}H and ^{13}C NMR spectra as well as elemental analysis .A clear assignment comes from IR vibrational frequency (1740-1750cm^{-1}) which are characteristic of –C=O Stretching of carbonyl of coumarins .

Table 1 ONE POT SYNTHESIS OF 3-ARYL-FURO[3,2-C]COUMARINS(4a-h)[a]

COMPOUNDS	R1	R2	% YIELD	M.P.^{0}c
4a	H	H	80	176
4b	H	CH3	82	165
4c	H	OCH3	82	163
4d	H	Cl	83	154
4e	H	Br	81	197
4f	H	NO2	82	203
4g	H	F	80	181
4h	Br	H	79	194

[a]Reaction condition:1) acetophenones(0.5mmol), 4-hydroxycoumarins (0.5mmol), NBS(0.5mmol), (PEG-400/water in (1:2) ratio at 80°C for 30 min.; [b]Isolated yield.

Characterization data of 3-aryl-furo[3,2-c]coumarins(4a-h)

3-phenyl-4H-furo[3,2-c]chromen-4-one(4a)-

IR(KBr,cm-1):1735(-C=O Stretch.),1638(s),^{1}H NMR(300 MHZ,$CDCl_3$,ppm):δ7.47-7.93(m,10H);^{13}C NMR ($CDCl_3$, 75 MHz rt) δ23.15(CH3), 107.6(S), 109.63(S), 113.1(d), 121.13(d), 123.9(d), 124.98(s), 125.2(s), 128.03(d), 128.5.(d),128.7(d),130.0(s),132.37(d),141.73(s),153.0(S),159.8(s),165.13(s,CO of coumarin). Anal .calculated for $C_{18}H_{12}O_3$ C,78.25;H,4.38% FOUND78.17;H,4.23%.

3-(p-tolyl)-4H- furo[3,2-c]chromen-4-one(4b)

IR(KBr,cm-1): 1741(-C=O Stretch.),1628,1129,955;^{1}H NMR(300 MHZ,$CDCl_3$,ppm); δ 2.45(S,3H,-CH_3),7.39-7.83(M,10H).13C NMR(CDCl3,75 MHz rt) δ23.15(CH3), 107.8(S), 113.73(S), 119.1(d), 120.13(d), 125.1(d), 126.58(s), 127.32(s), 128.53(d), 130.12(d), 131.73(d), 137.32(s), 142.37(d), 157.13(s), 159.38(s), 161.73(s, CO of coumarin). anal. calculated for $C_{18}H_{12}O_3$: C,78.25,H,4.38% FOUND78.17;H,4.23%

3-(4-methoxyphenyl)-4H-furo[3,2-c]chromen-4-one(4c)

IR(KBr,cm-1):3037,1728, (-C=O Stretch.),1559,1131;^{1}H NMR (300 MHZ,$CDCl_3$,ppm); δ3.92(S,3H,-OCH_3),7.12-7.98(m,9H);^{13}C NMR ($CDCl_3$,75 MHz rt) δ57.37(q,OCH_3), 107.3(S), 111.2(S), 113.7(d), 117.2(d), 122.31(d), 122.53(d),125.7(S),127.37(S),130.23(d),131.87(d), 142.3(d),153.21(S),159.37(S),160.3(S),160.82(CO of coumarin).anal.calculated for $C_{18}H_{12}O_4$: C,73.97;H,4.14% found C,73.93;H,4.13%.

3-(4-chlorophenyl)-4H-furo[3,2-c]chromen-4-one(4d)

IR(KBr,cm-1):3029,1749 (-C=O Stretch.),1638,1117;^{1}H NMR (300 MHZ,$CDCl_3$,ppm); δ 7.12-7.98(m,9H);^{13}C NMR ($CDCl_3$,75 MHz rt) δ109.3(S), 113.3(S), 114.3(d), 118.3(d), 123.21(d), 123.54(d), 124.3(S), 130.31(S), 131.1(d), 131.91(d), 148.9(d),153.41(S),156.47(S),159.1(S),162.82(s, CO of coumarin) anal. calculated for $C_{17}H_{19}O_3Cl$,67.48;H,3.16% found C,67.69,H,3.16%.

3-(4-bromophenyl)-4H-furo[3,2-c]chromen-4-one(4e)

IR (KBr,cm-1):3035,1751(-C=O Stretch.);^{1}H NMR (300 MHZ,$CDCl_3$,ppm); δ 7.29-7.99(m,9H);^{13}C NMR ($CDCl_3$,75 MHz rt) δ 111.3(S), 113.9(S), 115.3(d), 119.3(d), 121.1(d), 123.52(s), 125.3(S), 127.0(s), 128.42(d), 130.9(d), 132.31(d), 145.3(s), 153.21(S), 157.47(S), 159.3(S),(s,COof coumarin). anal. calculated for $C_{17}H_{19}O_3Br$, C,59.3021;H,2.6162% found C,59.28,H,2.6256%.

3-(4-nitrophenyl)-4H-furo[3,2-c]chromen-4-one(4f)

IR(KBr,cm-1):3027,1729 (-C=O Stretch.),1631,1341.7;^{1}H NMR (300 MHZ,$CDCl_3$,ppm); δ 7.503-7.78(m, 3H), 7.803-8.12(m, 4H), 8.131-8.518(d, 2H);^{13}C NMR ($CDCl_3$,75 MHZ rt) δ 112.1(S), 115.9(S), 117.3(d), 118.3(d), 122.1(d),124.13(d),126.23(S),127.15(S),129.0(d),131.31(d), 133.7(d), 144.31(S), 151.17(S), 156.7(S), 159.82 (s, CO of coumarin).anal. calculated for $C_{16}H_{19}NO_5$: C,65.08; H, 3.05% found C, 65.81, H, 2.96%.

3-(4-fluorophenyl)-4H-furo[3,2-c]chromen-4-one(4g)-

IR(KBr,cm-1):3033,1743.7 (-C=O Stretch.),1638.13,1113;^{1}H NMR (300 MHZ,$CDCl_3$,ppm); δ 7.09-7.912(m, 9H);^{13}C NMR ($CDCl_3$,75 MHz rt) δ109.28(S), 111.25(S), 117.8(d), 117.13(d), 120.3(d), 123.31(d), 127.14(d), 129.21(S),130.91(S),132.3(d),135.9(d), 145.1(d),153.21(S),159.37(S),163.2(S),(s,CO of coumarin).anal. Calculated for $C_{16}H_{19}O_3F$: C, 71.64; H, 3.35% found C, 73.09; H, 3.32%.

3-(2-bromophenyl)-4H-furo[3,2-c]chromen-4-one(4h)

IR(KBr,cm-1):3039,1749.7 (-C=O Stretch.),1632.13;^{1}H NMR (300 MHZ,$CDCl_3$,ppm); δ 8.13-7.32(m,9H);^{13}C NMR ($CDCl_3$,75 MHz rt) δ119.28(S), 121.25(S), 122.18(d), 123.13(d), 123.43(d), 124.31(d), 125.24(d), 126.21(S), 129.31(S), 130.1(d), 134.12(d), 135.2(d), 141.51(d), 145.22(d), 152.23(S), 159.97(S), 161.22(S), (s, CO of coumarin).anal. Calculated for $C_{16}H_{19}O_3Br$: C,59.3022; H, 2.616% found C, 60.109; H, 2.632%.

CONCLUSION

We have reported a facile, one pot ,efficient, convenient, environmentally benign protocol for the synthesis of 3-aryl-furo[3,2-C]coumarins via in situ generated α-Bromoketones. The notable features of this method are the used of safer PEG-400 and water as a non-volatile, greener reaction medium at 80^{o}C. and comparatively high yield.

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