“ONE-POT SYNTHESIS OF 3-PHENYL-FURO[3,2-C]COUMARINS IN PEG-400
AS A GREEN MEDIUM”

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Abstract:

We have developed convenient, eco-friendly, one-pot protocol for the synthesis of substituted 3-phenyl-furo[3,2-c]coumarins from in-situ generated \( \alpha \)-halo ketones and 4-hydroxy coumarins in PEG-400 as a greener solvent. The developed protocol provides the better alternative to the existing methods as it involves utilization of in-situ generated \( \alpha \)-halo ketones. The products obtained is characterized by using IR, 1H NMR, 13C NMR spectroscopy.

\textit{Scheme: 1}

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\includegraphics[width=0.8\textwidth]{scheme1.png}};
\node at (4.5,0) {PEG-400};
\node at (4.5,-0.5) {CH_3COOH/CH_3COONH_4};
\end{tikzpicture}
\end{center}

\textbf{SYNTHESIS OF 3-PHENYL-FURO[3,2-C]COUMARINS}

Keywords:

PEG-400, one-pot, green chemistry, 3-phenyl-furo[3,2-c]coumarins, Acetophenones

Introduction:

Furocoumarin derivatives are naturally occurring compounds and exhibit various biological activities such as antitumor, anti-inflammatory, antitumor, anticoagulant, antimicrobial, 


insecticidal, HIV inhibitory, anti-influenza, antioxidant these facts prompted us to design and develop new synthetic protocol for the synthesis of them [1-10].

Recently many improved methods designed to synthesis of furo[3,2-C]coumarins using piperidine/toluene).[11]using α-tosyloxyketones.[12]In this approach we have used user friendly N-bromosuccinimide for the bromination of various substituted acetophenones and avoid the use of lachrymatric, toxic and comparatively less stable α-halo ketones. PEG-400 is easily available, inexpensive, non-ionic liquid medium of low volatility, thermally stable, reusable, non-toxic 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].

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 phenacyl bromides and 4-hydroxy coumarins in PEG-400 as a greener medium to obtained high yield. In order to generate α-bromoacetophenones in situ we have carried out bromination of substituted acetophenones with N-bromosuccinimide in PEG-400 at ambient temperature. Main advantaged of this protocol is no need to isolate in situ generated lachrymatric α-bromo ketones and yield relatively high.

Result and Discussion

To determine the fate of proposal, we have carried out simple neat reaction of Acetophenone, NBS and stirred for 12 hr. at room temperature but it was observed that without use of PEG-400 reaction dose not proceed. when we used PEG-400 as a reaction medium followed by addition of solution of 4-Hydroxy coumarins in ACOH/ACONH4(4:1) yielded cycloaduct 3-phenyl-furo[3,2-C]coumarins in good to excellent yield (85-87%). all these compounds characterized by IR, 1H and 13C NMR spectra as well as elemental analysis. A clear assignment comes from IR vibrational frequency (1735-1745cm⁻¹) which are characteristic of −C=O Stretching of carbonyl of coumarins.
SYNTHESIS OF 3-PHENYL-FURO[3,2-C]COUMARINS

Material and method:

Acetophenones, NBS (N-bromosuccinimide) and 4-Hydroxycoumarin used in this work were used without further purification. All the chemicals and solvents were of AR grade and used without further purification. The completion of reactions were monitored with the help of thin layer chromatography using precoated aluminium sheets with GF254 silica gel, 0.2 mm layer thickness by E.Merck (Darmstadt, Germany). IR spectra were recorded on Shimadzu FT-IR-8400 instrument using KBr pellet method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using direct inlet probe technique. H NMR and C NMR was determined in DMSO-d6 solvent on a Bruker AC 400 MHz Spectrometer. Chemical shifts are reported in parts per million, melting points were taken in open capillary and are un-corrected.

General procedure for the preparation of 4(a-j)

A mix of aromatic acetophenones (0.5 mmol), NBS (0.55 mmol) in PEG-400 and was stirred for 6 hr. at R.T. The formation of α-Bromoketones was monitored by thin layer chromatography (TLC). After completion of bromination, add the solution of 4-hydroxy coumarin (0.5 mmol) and acetic acid and ammonium acetate (4:1) in PEG-400 and reaction mass further stirred for 2 hr. The progress of reaction was monitored by Thin layer chromatography (TLC). After completion of reaction product extracted with ethyl acetate (10×3). The combined Ethyl acetate phase was removed under reduced pressure to give corresponding 3-Aryl-furo[3,2-c]coumarins (4a-h) and mother liquor kept aside for further runs.
Table 1  one pot synthesis of of 3-ARYL-FURO[3,2-C]COUMARINS(4a-h)\(^a\)

<table>
<thead>
<tr>
<th>COMPOUNDS</th>
<th>R1</th>
<th>R2</th>
<th>% YIELD</th>
<th>M.P.(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>H</td>
<td>H</td>
<td>85</td>
<td>175</td>
</tr>
<tr>
<td>4b</td>
<td>H</td>
<td>CH3</td>
<td>86</td>
<td>164</td>
</tr>
<tr>
<td>4c</td>
<td>H</td>
<td>OCH3</td>
<td>85</td>
<td>163-165</td>
</tr>
<tr>
<td>4d</td>
<td>H</td>
<td>Cl</td>
<td>86</td>
<td>154-155</td>
</tr>
<tr>
<td>4e</td>
<td>H</td>
<td>Br</td>
<td>85</td>
<td>197-199</td>
</tr>
<tr>
<td>4f</td>
<td>H</td>
<td>NO2</td>
<td>87</td>
<td>203-205</td>
</tr>
<tr>
<td>4g</td>
<td>H</td>
<td>F</td>
<td>87</td>
<td>181</td>
</tr>
<tr>
<td>4h</td>
<td>Br</td>
<td>H</td>
<td>87</td>
<td>194-195</td>
</tr>
</tbody>
</table>

\(^a\)Reaction condition: 1) Acetophenones(0.5mmol), 4-hydroxycoumarins (0.5mmol), NBS(0.5mmol), in PEG-400; \(^b\)Isolated yield.

Characterization of Compounds (4a-h)

**COMPOUND 4a**-IR(KBr,cm-1): 1741(-C=O Stretch.), 1636(s), \(^1\)H NMR(300 MHZ,CDCl\(_3\),ppm): \(\delta\) 7.48-7.91(m,10H); 13C NMR(CDCl\(_3\),75 MHzrt) \(\delta\)23.14(CH3), 106.96(S), 109.16(S), 114.31(d), 122.23(d), 123.21(d), 124.19(s), 125.12(s), 128.23(d), 128.25(d), 128.17(d), 131.20(s), 132.57(d), 141.18(s), 153.12(S), 160.18(s), 165.03(s,CO of coumarin). anal.calculated for C\(_{18}\)H\(_{12}\)O\(_3\)C, 78.25; H, 4.38%FOUND78.17; H, 4.23%

**COMPOUND 4b**- IR(KBr,cm-1): 1739(-C=O Stretch.), 1638, 1123, 955\(^1\)H NMR(300 MHZ,CDCl\(_3\),ppm); \(\delta\) 2.55(S,3H,-CH3), 7.41-7.93(M,10H). 13C NMR(CDCl\(_3\),75 MHzrt) \(\delta\) 23.25(CH3), 107.18(S), 113.55(S), 119.21(d), 120.53(d), 125.58(d), 126.98(s), 127.73(s), 128.45(d), 131.22(d), 132.13(d), 137.52(s), 143.12(d), 157.54(s), 159.21(s), 160.73(s,CO of coumarin). anal.calculated for C\(_{18}\)H\(_{12}\)O\(_3\)C, 78.25, H, 4.38%FOUND78.27; H, 4.13%

**COMPOUND 4c**- IR(KBr,cm-1): 3037, 1728, (-C=O Stretch.), 1559, 1131;\(^1\)H NMR (300 MHZ,CDCl\(_3\),ppm); \(\delta\) 3.88(S,3H,-OCH3), 7.21-7.38(M,9H); 13C NMR (CDCl\(_3\),75 MHzrt)
δ57.27(q, OCH3), 106.93(S), 111.12(S), 114.27(d), 117.52(d), 123.11(d), 123.89(d), 125.27(S), 127.39(S), 130.47(d), 132.87(d), 142.58(d), 154.11(S), 159.77(S), 160.83(S), 161.18 (CO of coumarin).

COMPOUND 4d - IR(KBr, cm⁻¹): 3033, 1749 (-C=O Stretch.), 1632, 1127; ¹H NMR (300 MHz, CDCl₃, ppm); δ 7.25-7.87(m, 9H); ¹³C NMR (CDCl₃, 75 MHz rt)
δ109.13(S), 113.21(S), 114.35(d), 118.11(d), 122.21(d), 123.34(d), 124.14(S), 130.54(S), 131.41(d), 131.41(d), 148.49(d), 153.45(S), 156.85(S), 159.91(S), 162.14(s, CO of coumarin).

anal. calculated for C₁₇H₁₉O₃Cl, C, 67.48; H, 3.16% found C, 67.69, H, 3.18%.

COMPOUND 4e - IR (KBr, cm⁻¹): 3035, 1761 (-C=O Stretch.); ¹H NMR (300 MHz, CDCl₃, ppm); δ 7.25-7.87(m, 9H); ¹³C NMR (CDCl₃, 75 MHz rt)
δ111.13(S), 113.49(S), 115.53(d), 119.13(d), 122.41(d), 123.42(s), 126.23(S), 127.14(s), 129.42(d), 132.12(d), 145.73(s), 153.41(S), 157.67(S), 159.13(S), (s, CO of coumarin).

anal. calculated for C₁₇H₁₉O₃Cl, C, 59.85; H, 2.66% found C, 60.28, H, 2.98%.

COMPOUND 4f - IR(KBr, cm⁻¹): 3027, 1732 (-C=O Stretch.), 1342.7; ¹H NMR (300 MHz, CDCl₃, ppm); δ 7.55-7.88(m, 3H), 7.82-8.14(m, 4H), 8.13-8.48(d, 2H); ¹³C NMR (CDCl₃, 75 MHz rt)
δ108.98(S), 111.25(S), 117.58(d), 117.93(d), 121.35(d), 123.38(d), 127.54(d), 129.41(S), 131.11(S), 132.53(d), 134.79(d), 146.91(d), 153.91(S), 160.33(S), 163.42(S), (s, CO of coumarin). Anal. Calculated for C₁₆H₁₉NO₅ C, 65.08; H, 3.05% found C, 65.85, H, 2.93%.

COMPOUND 4g - IR(KBr, cm⁻¹): 3033, 1743.7 (-C=O Stretch.), 1342.7; ¹H NMR (300 MHz, CDCl₃, ppm); δ 7.19-7.98 (m, 9H); ¹³C NMR (CDCl₃, 75 MHz rt)
δ108.98(S), 111.25(S), 117.58(d), 117.93(d), 121.35(d), 123.38(d), 127.54(d), 129.41(S), 131.11(S), 132.53(d), 134.79(d), 146.91(d), 153.91(S), 160.33(S), 163.42(S), (s, CO of coumarin). Anal. Calculated for C₁₆H₁₉NO₅ F:C, 71.64; H, 3.35% found C, 73.11; H, 3.33%.
Conclusions:

We have reported a facile, one pot, efficient, 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 use of safer PEG-400 as a non-volatile, greener reaction medium at room temperature and avoid the use of lachrymatory α-haloketones and good to excellent yield.

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References:


