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Green synthesis of naphthiridinone using multicomponent reaction of Melderum's acid and 4-aminoquinoline-2-one

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Abstract: An efficient synthesis of naphthiridinone derivatives *via* reaction of 4-aminoquinoline-2-one, Melderum acid and ketones under solnent free conditions and room temperatureis described.

Keywords: Naphthiridinone; Acetophenone derivatives; Solvent-free**;** Meldrum's acid**;** 4-aminocoumarin, Dimethylcarbonate.

Introduction

Heterocyclic compounds hold a prominent position in medicinal chemistry owing to their wide spectrum of biological activities such as antimalarial [1], antimicrobial [2], antitumor [3], anticancer [4], antidepressant [5], antiviral [6], antidiabetic [7], anti-inflammatory [8] and anti-HIV. [9] Moreover, they also contribute in the feld of material science [10], dyes and pigment science [11] as well as agrochemistry [12]. Therefore, there is considerable thrust for the development of efficient synthetic strategies for producing these compounds. MCRs open diverse avenues to create novel concatenations in one pot fashion leading to diverse biologically potent heterocyclic scaffolds [13, 14]. Having a cascade of reactions occurring in one pot is highly beneficial in the context of modern trends for organic synthesis, where sustainability is as relevant as efficiency and selectivity. Multicomponent reactions being atom economic, efficient and extremely convergent in nature offer a number of advantages over stepwise sequential approaches [15–17]. In this work, the our purpose is finding out new procedures for synthesis of significant organic compounds, [18-25] we investigated a green procedure for the preparation of some naphthyridine derivatives 4 via the multicomponent reactions of 4-aminoquinoline-2-one **1**, Melderum's acid **2** and ketones derivatives **3** in the presence of Et_3N under solvent-free conditions at room temperature with excellent yields (Scheme 1).

Results and discussion

As part of our current studies [18-25] on the development of new routes to heterocyclic systems, we now report an efficient method to prepare functionalized naphthyridines. Thus the reaction of 4-aminoquinoline-2-one **1**, Melderum's acid **2** and ketones derivatives **3** in the presence of Et_3N at room temperature under solvent-free led to naphthyridines **5** in good yields (Scheme **1**).

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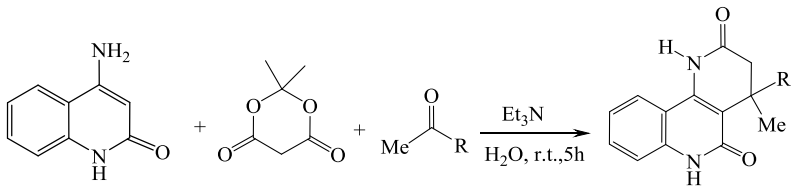


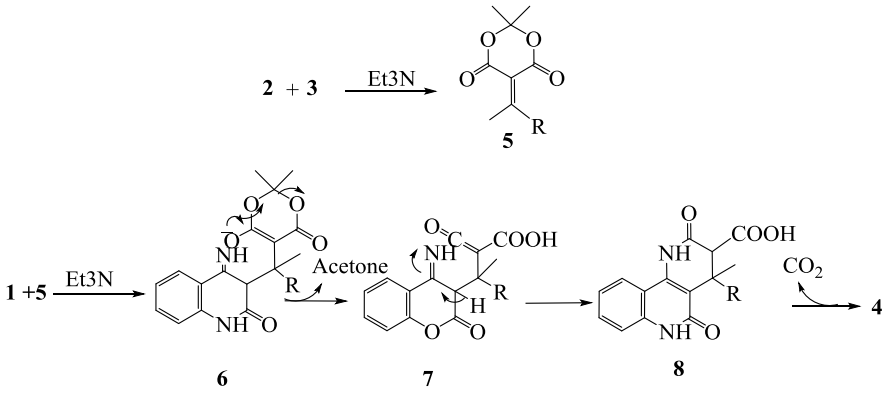
1 **2** **3** **4**

4	R	Yield/%
a	Me	97
b	Et	87
c	^{n}Pr	78
d	Me_2CHCH_2	65
e	Ph	90

Scheme 1. Synthesis of naphthyridine derivatives

Structures of compounds **4a**–**4d** were assigned by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. The ^{1}H NMR spectrum of **4a** showed two singlets arising from methyl and methylene protons, along with the aromatic protons. The ^{1}H NMR spectrum of **4a**–**4d** exhibited a characteristic AB system for the CH_2 moiety. The carbonyl group resonances in the ^{13}C NMR spectrum of **4a** appear at 159.5 and 164.8 ppm. The mass spectrum of **4a** displayed the molecular ion peak at *m*/*z* = 244.

A tentative mechanism for this transformation is proposed in Scheme 2. It is conceivable that the initial event is the formation of **5** which undergoes Knoevenagel condensation with Meldrum's acid. This intermediate is subsequently attacked by 4-aminoquinoline-2-one **1** to generate **6**. Intermediate **6** first loses acetone to give ketene **7**, which undergoes cyclization and decarboxylation to produce **4**.



Scheme 2. Proposed mechanism for the synthesis of naphthyridines **4**

Investigation of antioxidant activity using DPPH

Diphenyl-2-picrylhydrazyl (DPPH) radical scavenging test is broadly employed to estimate the ability of compounds to capture free radicals and their antioxidant activity in foods and biological systems. The DPPH analyze donating activity of the hydrogen atom (or one electron) and gives an evaluation of antioxidant activity because of free radical scavenging. The antioxidant activity of **4a-4d** was investigated by testing their ability to the DPPH radical. DPPH radical shows the absorption in area 517 nm but its absorption decreases when is reduced by an antioxidant or a radical species. In this study, the antioxidant activity of **4a-4d** was compared to BHT and TBHQ at different concentrations from 200 mmol/L to 1000 mmol/L. At all concentrations, the new synthesized compound **4a** had significant differences compared to BHT and TBHQ. Overall, the all compounds especially compound **4a** were shown excellent free radical

scavenging performance compared to BHT and TBHQ at 1000 ppm concentration

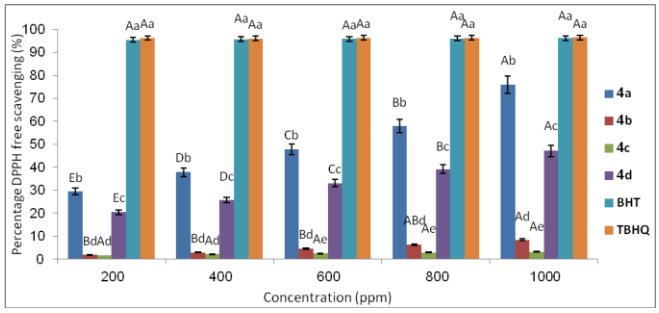


Figure 1. Order of antioxidant activity of **4a-4d** using DPPH

Ferric ions (Fe^{3+}) reducing potential (FRAP)

The ability of the synthesized compounds to reduce Ferric ions (Fe^{3+}) was studied by measuring the amount of exchange of Fe3+/ferricyanide complex to the Fe2+/ ferrous shape at 700 nm. The ability of compound to reducing may act as an important indicator of its potential antioxidant activity. Compound **4a** was displayed good reducing activity compared to standards (BHT and TBHQ).

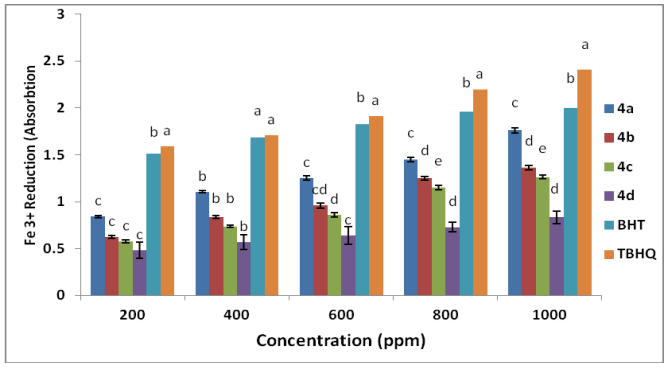


Figure 2. FRAP of compounds **4a-4d**

Conclusion

In conclusion, we have described a convenient route to naphthyridine derivatives from the reaction of 4-aminoquinoline-2-one **1**, Melderum's acid **2** and ketones derivatives **3** in the presence of Et_3N at room temperature under solvent-free conditions. The functionalized naphthyridine reported in this work may be considered as potentially useful synthetic intermediates because they possess atoms with different oxidation states. The advantage of the present procedure is that the reaction is performed under neutral conditions by simple mixing of the starting materials. The simplicity of the present procedure makes it an interesting alternative to other approaches.

Experiental

Material and methods

Mp: *Electrothermal-9100* apparatus; uncorrected. IR Spectra: *Shimadzu IR-460* spectrometer. ^{1}H- and ^{13}C-NMR spectra: Bruker DRX-500 AVANCE instrument; in $CDCl_3$ at 500.1 and 125.7 MHz, resp.; □ in ppm, *J* in Hz. EI-MS (70 eV): Finnigan-MAT-8430 mass spectrometer, in *m/z*. Elemental analyses (C, H, N) were performed with a Heraeus CHN-O-Rapid analyzer. All chemicals were used as-received from the appropriate suppliers.

General procedure

To a stirred mixture of Meldrum's acid **2** (0.29 g, 2 mmol) and methyl ketones **3** (2 mmol) was added Et_3N (2 mmol). The reaction mixture was stirred for 3 hours. After completion of the reaction (monitored by TLC), was added 4-aminoquinoline-2-one **1** (2 mmol) to previous mixture. The reaction mixture was stirred for 1 h. After completion of the reaction (monitored by TLC), 15 mL water was poured to the mixture and the solid residue was purified by column chromatography (SiO_2; hexane/AcOEt) to afford **4.**

4,4-Dimethyl-3,4-dihydro-2H,5H-pyrano[3,2-c] naphthyridine -2,5-dione (4a):

White powder, yield: 0.47 g (97%), m.p. 128-131°C. IR (KBr) (ν_{max}/cm^{-1}): 1794, 1712, 1626, 1358 cm^{-1}. ^{1}H NMR: 1.98 (s, 6 H, 2 Me), 3.23 (s, 2 H, CH_2), 7.80 (t, ^3J = 8.1 Hz, 1 H, CH), 7.81 (d, ^3J = 7.6 Hz, 1 H, CH), 8.06 (td, ^3J = 8.56 Hz, ^4J = 1.15 Hz, 1 H, 1 CH), 7.81 (d, ^3J = 7.8 Hz, 1 H, CH).^{13}C NMR: 26.5 (2 Me), 33.8 (C), 44.3 (CH_2), 111.1 (C), 114.0 (C), 116.4 (CH), 123.1 (CH), 124.4 (CH), 132.6 (CH), 152.7 (C), 156.0 (C), 159.5 (C=O), 164.8 (C=O). EI-MS: 245 (M^++1, 95), 244 (M^+, 85), 229 (65), 216 (45), 201 (100), 121 (50), 92 (40). Anal. Calcd for $C_{14}H_{12}O_4$ (244.24): C 68.85, H 4.95%. Found: C 68.10, H 5.01%.

4-Ethyl-4-methyl-3,4-dihydro-2H,5H-pyrano[3,2-c] naphthyridine -2,5-dione (4b):

White powder, yield: 0.45 g (87%), m.p. 100-103 °C. IR (KBr) (ν_{max}/cm^{-1}): 1796, 1716, 1624, 1377 cm^{-1}. ^{1}H NMR: 1.33 (t, ^3J = 7.5 Hz, 3 H, Me), 1.92 (s, 3 H, Me), 2.06 (dq, ^2J = 6.7 Hz, ^3J = 7.4 Hz, 1 H, CH), 2.56 (dq, ^2J = 6.7 Hz, ^3J = 7.4 Hz, 1 H, CH), 3.07 (d, ^2J = 15.9 Hz, 1 H, CH), 3.30 (d, ^2J = 15.9 Hz, 1 H, CH), 7.74-7.77 (m, 2 H, 2 CH), 8.02 (td, ^3J = 7.35 Hz, ^4J =

1.55 Hz, 1 H, 1 CH), 8.26 (dd, ^3J = 8.1 Hz, ^4J = 1.45 Hz, 1 H, CH).^{13}C NMR: 8.90 (Me), 25.3 (Me), 31.7 (CH_2), 37.6 (C), 40.9 (CH_2), 109.6 (C), 113.6 (C), 116.3 (CH), 122.9 (CH), 124.3 (CH), 132.6 (CH), 152.7 (C), 156.8 (C), 159.5 (C=O), 165.3 (C=O). EI-MS: 259 (M^++1, 95), 258 (M^+, 85), 243 (74), 230 (42), 215 (100), 121 (44), 92 (42). Anal. Calcd for $C_{15}H_{14}O_4$ (258.27): C 69.76, H 5.46%. Found: C 69.22, H 5.40%.

4-Methyl-4-propyl-3,4-dihydro-2H,5H-pyrano[3,2-c] naphthyridine -2,5-dione (4c):

White powder, yield: 0.42 g (87%), m.p. 87-93 °C. IR (KBr) (ν_{max}/cm^{-1}): 1794, 1710, 1622, 1358 cm^{-1}. ^{1}H NMR: 1.36 (t, ^3J = 7.3 Hz, 3 H, Me), 1.64-1.79 (m, 2 H, CH_2), 1.95 (s, 3 H, Me), 2.01 (dt, ^2J = 4.4 Hz, ^3J = 12.8 Hz, 1 H, CH), 2.48 (dt, ^2J = 4.4 Hz, ^3J = 12.8 Hz, 1 H, CH), 3.09 (d, ^2J = 15.9 Hz, 1 H, CH), 3.31 (d, ^2J = 15.9 Hz, 1 H, CH), 7.75-7.78 (m, 2 H, 2 CH), 8.02 (td, ^3J = 8.8 Hz, ^4J = 1.4 Hz, 1 H, 1 CH), 8.27 (dd, ^3J = 8.0 Hz, ^4J = 1.2 Hz, 1 H, CH). ^{13}C NMR: 14.3 (Me), 17.9 (Me), 25.7 (CH_2), 37.4 (C), 41.4 (CH_2), 41.5 (CH_2), 109.9 (C), 113.6 (C), 116.4 (CH), 123.0 (CH), 124.3 (CH), 132.5 (CH), 152.7 (C), 156.6 (C), 159.5 (C=O), 165.2 (C=O). EI-MS: 273 (M^++1, 95), 272 (M^+, 85), 257 (65), 244 (58), 229 (100), 121 (60), 92 (42). Anal. Calcd for $C_{16}H_{16}O_4$ (272.30): C 70.58, H 5.92%. Found: C 69.22, H 5.59%.

4-Isobutyl-4-methyl-3,4-dihydro-2H,5H-pyrano[3,2-c]naphthyridine-2,5-dione (4d):

White powder, yield: 0.37 g (65%), m.p. 107-108°C. IR (KBr) (ν_{max}/cm^{-1}): 1797, 1710, 1620, 1359 cm^{-1}. ^{1}H NMR: 0.93 (d, ^3J = 6.6 Hz, 3 H, Me), 0.97 (d, ^3J = 6.6 Hz, 3 H, Me), 1.56 (s, 3 H, Me), 1.59 (dd, ^2J = 5.3 Hz, ^3J = 14.4 Hz, 1 H, CH), 1.70-1.75 (m, 1 H, CH), 2.04 (dd, ^2J = 5.3 Hz, ^3J = 14.4 Hz, 1 H, CH), 2.69 (d, ^2J = 15.9 Hz, 1 H, CH), 2.96 (d, ^2J = 15.8 Hz, 1 H, CH), 7.35-7.38 (m, 2 H, 2 CH), 7.62 (td, ^3J = 7.37 Hz, ^4J = 1.5 Hz, 1 H, 1 CH), 7.89 (dd, ^3J = 7.9 Hz, ^4J = 1.5 Hz, 1 H, CH). ^{13}C NMR: 24.7 (Me), 25.3 (CH), 25.6 (Me), 26.7 (Me), 37.9 (C), 42.4 (CH_2), 47.7 (CH_2), 111.2 (C), 114.0 (C), 116.9 (CH), 123.5 (CH), 124.7 (CH), 133.0 (CH), 153.1 (C), 156.7 (C), 160.1 (C=O), 165.7 (C=O). EI-MS: 287 (M^++1, 80), 244 (M^+, 68), 272 (65), 259 (45), 244 (100), 121 (50), 92 (30). Anal. Calcd for $C_{17}H_{18}O_4$ (286.32): C 71.31, H 6.34%. Found: C 71.0, H 6.22%.

References

[1] Cagniant, P. Cagniant, D. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R.; Boulton, A. J.; Eds.; Academic Press: New York, 1975 Vol.18, p 337. Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao. G. Q.; Barluenga, S.; Mitchell, H. J. (2000) Natural Product-like Combinatorial Libraries Based on Privileged Structures.

[2] Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G.-Q.; Barluenga, S.and Mitchell H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939.

[3] Green, G. R; Evans, J. M.; Vong., A. K. in *Comprehensive Heterocyclic Chemistry II*: Katritzky, A. R.; Rees, C. W.; Scriven, E. F.; Eds.; Pergamon Press, Oxford, 1995, Vol. 5, p. 469.

[4] Foye, W.O. *Principi Di Chemico Frmaceutica, Piccin*, Padova, Italy, 1991.

[5] Konkoy, C. S.; Fick, D. B.; Cai, S. X.; Lan, N. C.; Keana, J. F. W.; *PCT Int Appl WO* 0075123, **2000**, *Chem. Abstr.* **2001**, *134*, 29313a.

[6] (a) Pastine, S. J.; Youn, S. W.; Sames, D. *Org. Lett.* **2003**, *5*, 1055. (b) Youn, S. W.; Pastine, S. J.; Sames, D. *Tetrahedron* **2003**, *59*, 8859. (c) Hardouin, C.; Burgaud, L.; Valleix, A.; Doris, E. *Tetrahedron Lett.* **2003**, *44*, 435. (d) Shi, L.; Narula, C. K.; Mak, K. T.; Kao, L.; Xu, Y.; Heck, R. F. *J. Org. Chem.* **1983**, *48*, 3894.

[7] Kuwada, T.; Harada, K.; Nobuhiro, J.; Choshi, T. *Heterocycles* **2002**, *57*, 2081.

[8] Wang Q.; Finn M. G. *Org. Lett.* **2000**, *2*, 4063.

[9] Broom, A. D.; Shim, J. L.; Anderson, G. L. *J. Org. Chem*. **1976**, *41*, 1095.

[10] Yu, N.; Aramini, J. M.; Germann, M. W.; Huang, Z. *Tetrahedron Lett.* **2000**, *41*, 6993.

[11] Sheibani, H.; Mosslemin M. H.; Behzadi, S.; Islami, M. R.; Saidi, K. *Synthesis* **2006**, 435.

[12] Lacova, M.; Stankovicova, H.; Boha, A.; Kotzianova, B. *Tetrahedron* **2008**, *64*, 9646.

[13] Ahluwalia, V. K.; Kumar, R.; Khurana, A.; Bhatla, R. *Tetrahedron* **1990**, *46*, 3953.

[14] Abdolmohammadi, S.; Balalaie, S. *Tetrahedron Lett*. **2007**, *48*, 3299.

[15] Yavari, I.; Hossaini, Z.; Sabbaghan, M. *Tetrahedron Lett.* **2006**, *47*, 6037.

[16] Yavari, I.; Sabbaghan, M.; Hossaini, Z. *Molecular Diversity* **2007**, *11*, 1.