Short communication

A Facile One-Pot Synthesis of Functionalized 4,8-Dihydropyrano[3,2-b]-pyran-4-ones

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Abstract

The reactive intermediates generated by the addition of alkyl isocyanides and dialkyl acetylenedicarboxylates were trapped by 5-hydroxy-2-hydroxymethyl-4*H*-pyran-4-one (kojic acid) to yield functionalized 4,8-dihydropyrano[3,2-*b*]-pyran-4-ones at ambient temperature in good yields.

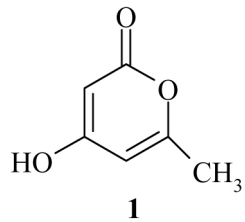
Keywords: Kojic acid, dialkyl acetylenedicarboxylate, *tert*-butyl isocyanide, cyclohexyl isocyanide, 4,8-dihydropyrano[3,2-*b*]pyran-4-one.

1. Introduction

There has been particular attention in chromenes and their derivatives due to their application in industry, biology, and synthesis.[1–3] Most interest arises because of the bicyclic ring in this system which has motivated many chemists to prepare this valuable compound through different routes.[4–5] Recently, the synthesis of various derivatives of fused pyran-2-one has received much attention due to their utilization as HIV protease inhibitors in nonpeptide human immunology.[6] The fused pyran derivatives have been synthesized using a number of methods.[7] Teimouri and coworkers[8] reported a three-component reaction of 4-hydroxy-6-methyl-2*H*-pyran-2-one (**1**), a 2-pyrone derivative, with an acetylenic ester in the presence of an alkyl isocyanide to obtain the corresponding fused pyran. These results inspired us to study this type of reaction with kojic acid (5-hydroxy-2-hydroxymethyl-4*H*-pyran-4-one, **2**), as a 4-pyrone derivative, which is an inexpensive naturally available compound. Additionally, as part of our current studies on the development of new routes to prepare heterocyclic systems,[9–11] we performed this annulation reaction using kojic acid as a source of OH-acid.

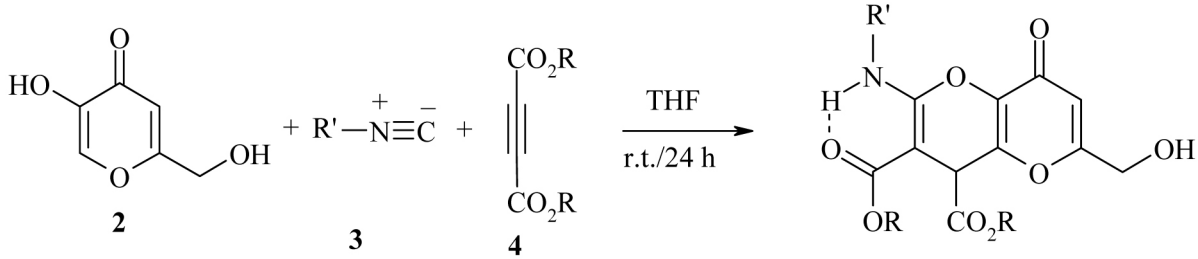
2. Results and Discussion

When an equimolar amount of *tert*-butyl isocyanide was slowly added to a mixture of 1:1 molar ratio of kojic acid and dimethyl acetylenedicarboxylate at ambient tem-



1

3,5	R	R'	Yield (%) of **5**
a	Me	^{t}Bu	80
b	Et	^{t}Bu	80
c	^{t}Bu	^{t}Bu	75
d	Me	^{c}Hex	75
e	Et	^{c}Hex	75

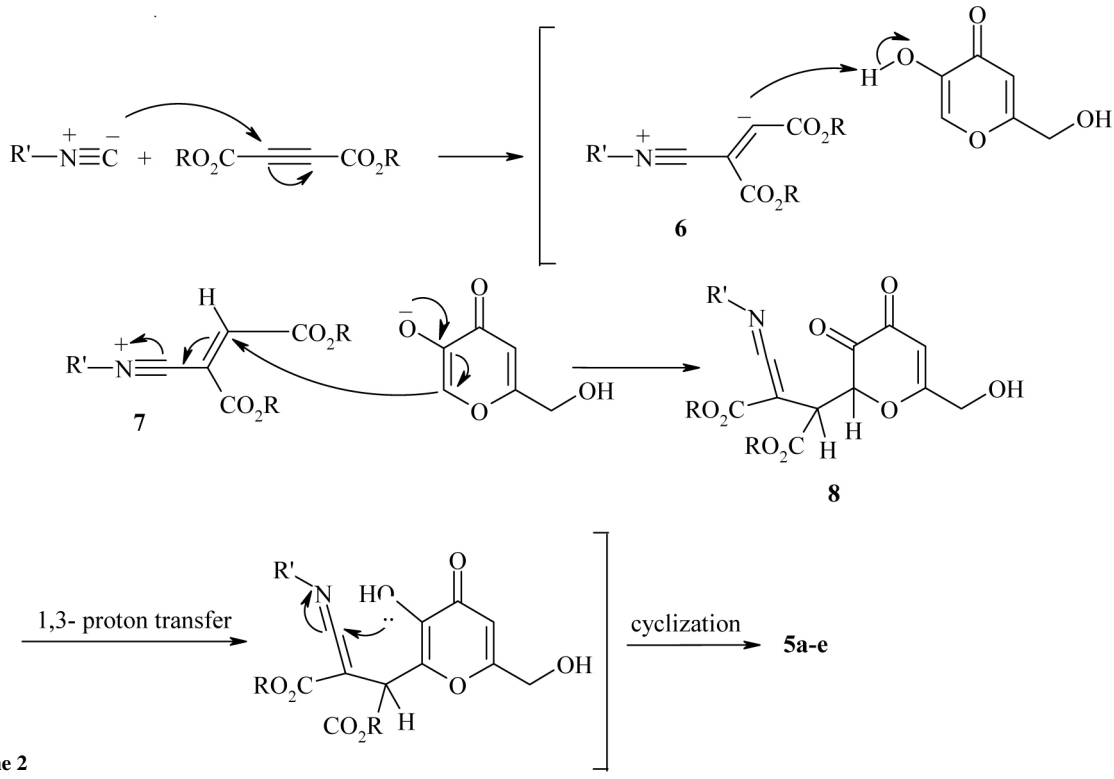


2 **3** **4** **5a-e**

Scheme 1

perature, after 24 h compound **5a** was obtained in 80% yield (Scheme 1). In order to determine the generality of this reaction the experiments were successfully repeated by using various derivatives of alkyl isocyanides and acetylenic esters as presented in Scheme 1.

On the basis of the well-established chemistry of isocyanides,[12–17] nucleophilic addition of alkyl isocyanide **3** to dialkyl acetylenedicarboxylate **4** leads to zwitterionic intermediate **6** which is protonated by kojic acid to give intermediate **7**. This intermediate is attacked by kojic acid anion to produce ketenimine **8**. 1,3-proton transfer in compound **8** and subsequent cyclization forms products **5a-e** (Scheme 2).



Scheme 2

The structures of compounds **5a-e** were deduced from their ^{1}H and ^{13}C NMR, IR and mass spectra, and elemental analysis. The ^{1}H NMR spectrum of **5a** exhibited a singlet at 1.47 ppm for the *tert*-butyl group, two singlets at 3.69 and 3.72 ppm for two methoxy groups, a singlet at 4.61 ppm for methine proton ($CHCO_2Me$) and two broad signals at 4.00 and 8.72 ppm for OH and NH protons, respectively. The proton-decoupled ^{13}C NMR spectrum of **5a** showed 15 distinct resonances in agreement with the proposed structure. Polarization of the C_2-C_3 double bond by the oxo and amino groups in the dihydropyrano ring led to appearance of C_2 and C_3 absorptions at 170.6 ppm and at 70.7 ppm, respectively. The IR spectrum of **5a** displayed two absorption bands at 3450 and 3250 cm^{-1} indicating the presence of amine and alcohol groups, and strong bands at 1733 and 1666 cm^{-1} for C=O groups, respectively. The mass spectrum of **5a** displayed a molecular ion peak at m/z 367, which was consistent with the 1:1:1 adduct of *tert*-butyl isocyanide, dimethyl acetylenedicarboxylate and kojic acid.

The ^{1}H and ^{13}C NMR spectra of compounds **5b-e** were similar to those of **5a**, except for the ester and amine moieties, which exhibited characteristic signals with appropriate chemical shifts for the specific substitution patterns.

3. Conclusion

We have developed a convenient, one-pot method for preparing functionalized 4,8-dihydropyrano[3,2-*b*]pyran-4-ones. In the present method substrates react without any prior activation or modification. The simplicity of the procedure makes it an interesting alternative to complex multistep approaches.

4. Experimental

Dialkyl acetylenedicarboxylates, *tert*-butyl isocyanide, cyclohexyl isocyanide and kojic acid were obtained from Fluka and were used without further purification. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. ^{1}H and ^{13}C, NMR spectra were measured with Bruker DRX-500 and 400 Avance spectrometers. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization

potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. Elemental analyses were performed using a Heraeus CHN-O Rapid analyzer.

Typical procedure for synthesis of dimethyl 2-(*tert*-butylamino)-6-(hydroxymethyl)-8-oxo-4,8-dihydropyrano[3,2-b]pyran-3,4-dicarboxylate (5a).

To a stirred solution of kojic acid (0.28 g, 2.0 mmol) and dimethyl acetylenedicarboxylate (0.24 ml, 2.0 mmol) in THF (10 ml) was dropwisely added *tert*-butyl isocyanide (0.32 g, 2.0 mmol) at –10 °C over 10 min. The reaction mixture was then allowed to warm up to room temperature and stirred for 24 h. The solvent was removed under reduced pressure and the residue purified by column chromatography (Merck Silica gel, 230–400 mesh) using hexane:ethyl acetate (60:40) as eluent to give pure product **5a** as a yellow powder in 80% yield.

4. 1. Analytical Data for Compounds 5a-e:

Dimethyl 2-(*tert*-butylamino)-6-(hydroxymethyl)-8-oxo-4,8-dihydropyrano [3,2-*b*]pyran-3,4-dicarboxylate (5a). Yellow powder, m.p. 160–163 °C, yield 80%, ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.47 (9H, s, C*Me*$_3$), 3.69 and 3.72 (6H, 2s, 2OMe), 4.00 (1H, bs, OH), 4.49 (2H, s, OCH_2), 4.61 (1H, s, CH), 6.53 (1H, s, vinyl proton), 8.72 (1H, bs, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.1 (C*Me*$_3$), 41.6 (CH), 51.1 and 52.9 (2OMe), 53.3 (N*C*Me$_3$), 60.6 (OCH_2), 70.7 (C), 112.5 (CH), 137.9, 147.1, 160.1 and 170.6 (4C), 167.3 and 168.9 (2C=O, esters), 170.7 (C=O, ketone); IR (KBr) ν 3450 (NH), 3250 (OH), 1733 and 1666 cm^{-1} (C=O); MS: m/z (%): 367 ($M^{+\cdot}$, 4), 308 (85), 252 (100), 220 (28), 192 (9), 57 (10). Anal. Calcd. for $C_{17}H_{21}NO_8$ (367.36): C, 55.58; H, 5.76; N, 3.81. Found: C, 55.45; H, 5.69; N, 3.77.

Diethyl 2-(*tert*-butylamino)-6-(hydroxymethyl)-8-oxo-4,8-dihydropyrano[3,2-*b*]pyran-3,4-dicarboxylate (5b). Yellow powder, m.p. 142–145 °C, yield 80%, ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (3H, t, $^3J_{HH}$=7.1 Hz, CH_3), 1.26 (3H, t, $^3J_{HH}$=7.1 Hz, CH_3), 1.47 (9H, s, C*Me*$_3$), 3.5 (1H, bs, OH), 4.10–4.20 (4H, m, 2OCH_2), 4.48 (2H, s, OCH_2), 4.60 (1H, s, CH), 6.51 (1H, s, vinyl proton), 8.72 (1H, bs, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1 and 14.4 (2CH_3) 30.1 (C*Me*$_3$), 41.8 (CH), 53.2 (N*C*Me$_3$), 59.7, 60.6 and 61.9 (3OCH_2), 70.7 (C), 112.5 (CH), 137.8, 147.1, 159.9 and 170.5 (4C), 167.0 and 168.6 (2C=O, esters), 170.6 (C=O, ketone); IR (KBr) ν 3413 (NH), 3276 (OH), 1744 and 1674 cm^{-1} (C=O); MS: m/z (%): 395 ($M^{+\cdot}$, 3), 322 (81), 266 (100), 238 (19), 220 (25), 57 (21). Anal. Calcd. for $C_{19}H_{25}NO_8$ (395.37): C, 57.72; H, 6.37; N, 3.54. Found: C, 57.61; H, 6.32; N, 3.50.

Di-*tert*-butyl 2-(*tert*-butylamino)-6-(hydroxymethyl)-8-oxo-4,8-dihydropyra-no[3,2-*b*]pyran-3,4-dicarboxylate (5c). Yellow powder, m.p. 150–152 °C, yield 75%, ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44, 1.47 and 1.48 (27H, 3s, 3C*Me*$_3$), 4.09 (1H, bs, OH), 4.45 (1H, s, CH), 4.49 (2H, s, OCH_2), 6.50 (1H, s, vinyl proton), 8.65 (1H, bs, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.9, 28.5 and 30.2 (3C*Me*$_3$), 43.3 (CH), 52.9 (N*C*Me$_3$), 60.6 (OCH_2), 72.3 (C), 79.8 and 82.1 (2O*C*Me$_3$), 112.3 (CH), 137.7, 148.1, 159.8 and 169.7 (4C), 167.1 and 168.3 (2C=O, esters), 170.8 (C=O, ketone); IR (KBr) ν 3509 (NH), 3250 (OH), 1739 and 1658 cm^{-1} (C=O); MS: m/z (%): 451 ($M^{+\cdot}$, 2), 350 (46), 294 (92), 238 (100), 220 (13), 176 (16), 57 (60). Anal. Calcd. for $C_{23}H_{33}NO_8$ (451.52): C, 61.18; H, 7.37; N, 3.10. Found: C, 61.10; H, 7.32; N, 3.06.

Dimethyl 2-(cyclohexylamino)-6-(hydroxymethyl)-8-oxo-4,8-dihydropyrano [3,2-*b*]pyran-3,4-dicarboxylate (5d). White powder, m.p. 158–161 °C, yield 75%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22–2.02 (10H, m, 5CH_2), 3.09 (1H, bs, OH), 3.72 and 3.74 (6H, 2s, 2OMe), 3.90–3.99 (1H, m, CH), 4.52 (2H, s, OCH_2), 4.63 (1H, s, CH), 6.53 (1H, s, CH), 8.64 (1H, bs, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.2, 24.2, 25.4, 33.4 and 33.5 (5CH_2), 41.7 (CH), 49.9 (NCH), 51.1 and 53.0 (2OCH_3), 60.7 (OCH_2), 70.0 (C), 112.7 (CH), 137.9, 147.1, 158.7 and 170.5 (4C), 166.6 and 168.8 (2C=O, esters), 170.8 (C=O, ketone); IR (KBr) ν 3415 (NH), 3312 (OH), 1742 and 1684 cm^{-1} (C=O); MS: m/z (%): 393 ($M^{+\cdot}$, 3), 334 (100), 252 (64), 220 (15), 192 (4), 83 (3). Anal. Calcd. for $C_{19}H_{23}NO_8$ (393.40): C, 58.01; H, 5.89; N, 3.56. Found: C, 59.17; H, 6.01; N, 3.65.

Diethyl 2-(cyclohexylamino)-6-(hydroxymethyl)-8-oxo-4,8-dihydropyrano[3,2-*b*]pyran-3,4-dicarboxylate (5e). White powder, m.p. 133–136 °C, yield 75%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (3H, t, $^3J_{HH}$=7.2 Hz, CH_3), 1.27 (3H, t, $^3J_{HH}$=7.2 Hz, CH_3), 1.31–2.02 (10H, m, 5CH_2), 2.98 (1H, bs, OH), 3.94–3.97 (1H, m, CH), 4.10–4.25 (4H, m, 2OCH_2), 4.51 (2H, s, OCH_2), 4.62 (1H, s, CH), 6.52 (1H, s, CH), 8.64 (1H, bs, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 and 14.4 (2CH_2), 24.2, 24.2, 25.4, 33.4 and 33.5 (5CH_2), 41.9 (CH), 49.8 (NCH), 59.6, 60.8 and 61.8 (3OCH_2), 70.1 (C), 112.7 (CH), 137.8, 147.2, 158.6 and 170.5 (4C), 166.4 and 168.5 (2C=O, esters), 170.5 (C=O, ketone); IR (KBr) ν 3411 (NH), 3336 (OH), 1743 and 1673 cm^{-1} (C=O); MS: m/z (%): 421 ($M^{+\cdot}$, 3), 348 (100), 266 (86), 220 (27), 192 (7), 83 (13). Anal. Calcd. for $C_{21}H_{27}NO_8$ (421.45): C, 59.86; H, 6.46; N, 3.32. Found: C, 61.01; H, 6.59; N, 3.39.

5. References

1. G. R. Geen, J. M. Evans, A. K. Vong, in: A. R. Katritzky, C. W. Rees, E. F. V. Scriven, (Eds.): *Comprehensive Heterocyclic Chemistry*, 1st Ed., Pergamon, New York, **1996**, *Vol. 5*, 469–500.
2. H. Miao, Z. Yang, *Org. Lett.* **2000**, *2*, 1765–1768.

3. P. Kumar, M. S. Bodas, *Org. Lett.* **2000**, *2*, 3821–3823.
4. K. A. Parker, T. L. Mindt, *Org. Lett.* **2001**, *3*, 3875–3878.
5. a) B. A. Chauder, C. C. Lopes, R. S. C. Lopes, A. J. M. Dasilva, V. Snieckus, *Synthesis* **1998**, 279–282. b) E. E. Schweizer, T. Minami, D. M. Crouse, *J. Org. Chem.* **1971,** *36*, 4028–4032.
6. a) S. Wang, G. W. A. Milne, X. Yang, I. J. Posey, M. C. Nicklaus, L. Graham, W. G. Rice, *J. Med. Chem.* **1996**, *39*, 2047–2054. b) L. Pochet, C. Doucet, M. Schynts, N. Thierry, N. Boggetto, B. Pirotte, K. Y. Jiang, B. Masereel, P. D. Tullio, J. Delarge, M. Reboud-Ravaux, *J. Med. Chem.* **1996**, *39*, 2579–2585. c) A. Mazumder, S. Wang, N. Neamati, M. Nicklaus, S. Sunder, J. Chen, G. W. A. Milne, W. G. Rice, Jr, T. R. Burke, Y. Pommier, *J. Med. Chem.* **1996**, *39*, 2472–2481.
7. a) J. L. Soto, S. Seoane, N. Martin, M. Quinteiro, *Heterocycles* **1984**, *22*, 1–6. b) N. Martin, A. Martinez-Grau, C. Seoane, J. L. Marco, *Tetrahedron Lett.* **1993**, *35*, 5627–5630. c) M. Moreno-Mañas, R. Pleixats, *Heterocycles* **1994**, *37*, 585–601.
8. M.B. Teimouri, R. Bazhrang, V. Eslamimanesh, A. Nouri, *Tetrahedron* **2006**, *62*, 3016–3020.
9. S. Asghari, M. Qandalee, *Acta. Chim. Solv.* **2007**, *54*, 638–641.
10. S. Asghari, M. Tajbakhsh, V. Taghipour, *Tetrahedron Lett.* **2008**, *49*, 1824–1827.
11. S. Asghari, M. Qandalee, A. Salimi, *Monatsh. Chem.* **2008**, *139*, 1217–1222.
12. I. Ugi, *Isonitrile Chemistry*; Academic: London, **1971**.
13. I. Ugi, *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 810–819.
14. A. Domling, I. Ugi, *Angew. Chem. Int. Ed. Engl.* **2000**, *39,* 3168–3210.
15. H. M. Walborsky, M. P. Periasamy, In *The Chemistry of Functional Groups*, S. Patai and Z. Rappoport (Eds.), Wiley, New York **1983**, Chapter 20.
16. S. Marcaccini, T. Torroba, *Org. Prep. Proced.* **1993**, *25*, 141–208.
17. A. Domling, *Chem. Rev.* **2006**, *106*, 17–89.

Povzetek

V prispevku je predstavljena priprava substituiranih 4,8-dihidropiran[3,2-*b*]-piran-4-onov z lovljenjem intermediatov, ki nastanejo pri adiciji alkil izocianidov in dialkil acetilendikarboksilatov na 5-hidroksi-2-hidroksimetil-4*H*-piran-4-on (kojsko kislino). Reakcija poteka pri sobni temperaturi z dobrimi izkoristki.