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Improved preparation and structural investigation of 4-aryl-4-oxo-2-hydroxy-2-butenoic acids and methyl esters

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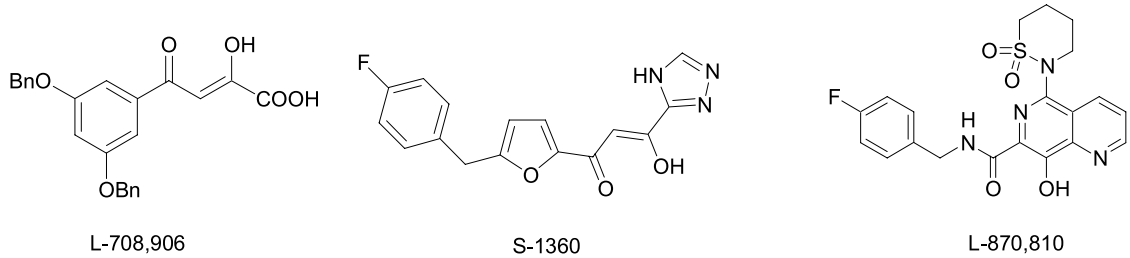
Abstract—A simple and efficient oxalylation of aryl methyl ketones was accomplished with dimethyl oxalate in the presence of sodium methoxide. The unpreviously reported sodium ketoenolate esters were isolated and gently hydrolyzed into the ketoenol esters in good yields. Alternatively the sodium ketoenolate esters hydrolysis could also be conducted to directly afford the ketoenol acids, which represent one of the most promising class of HIV-1 integrase inhibitors. Advantages over previously reported procedures were better yields and simplicity of the purification protocol.

1. Introduction

Human immunodeficiency virus type 1 (HIV-1) is the etiological agent of AIDS. The replicative cycle of this retrovirus has been intensively studied in order to identify targets and design specific inhibitors. To date, Food and Drug Administration approved drugs target reverse transcription (inhibition of reverse transcriptase), protein synthesis (inhibition of protease) and fusion (interaction with glycoprotein 41).[1] Persistence of latent HIV-1 in resting memory CD4+T cells, emergence of resistant HIV strains, drug toxicity and expensive medication have led to the development of novel drugs which interact with other viral replication processes. Integrase that catalyzes the insertion of the proviral DNA into the genome of the host cell, has emerged as an attractive target because it is necessary for stable infection and counterpart enzymes are lacking in the host.

Among numerous classes of molecules,[2] β-diketoacid containing inhibitors (their usual name is DKAs but their structures correspond to 4-aryl-(or 4-styryl-)[3] 4-oxo-2-hydroxy-2-butenoic acids, see Scheme 1) have emerged as the most promising drug candidates,[4] which are selective for integrase. S-1360[5] from Shionogi Company and L-708,906[6,7] from Merck Company are the best examples of this family, S-1360 being one of the only two currently available integrase inhibitors under clinical studies. Starting with this β-diketoacid structure, novel 8-hydroxynaphthyridine derivatives[8] have been designed and L-870,810 is under clinical evaluation.[9]

The synthesis of 4-aryl-4-oxo-2-hydroxy-2-butenoic acids **4** was achieved by the oxalylation of the corresponding aryl methyl ketones **1** in the presence of base followed by either alkaline or acidic hydrolysis (Scheme 2).[10–16] The



L-708,906 S-1360 L-870,810

Scheme 1.

Keywords: HIV integrase inhibitors; Tautomerism; Antiviral agents; Diketoacids.
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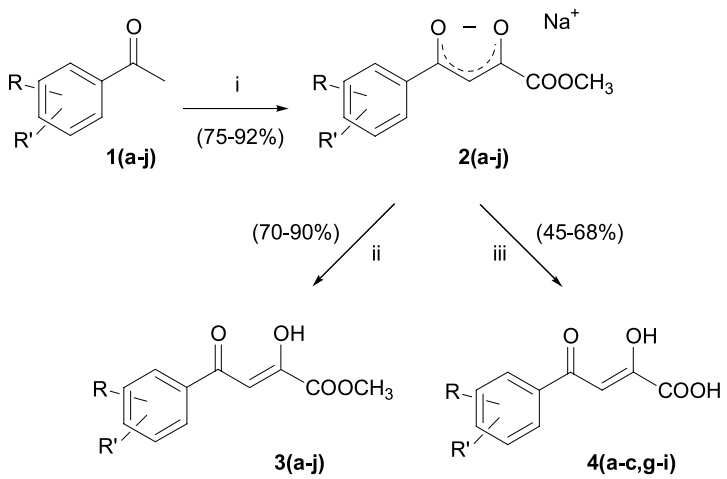


Scheme 2. Reagents and conditions: (i) dimethyl oxalate (1 equiv.) in Et_2O, then 2 M MeONa in MeOH, 1 h 30, rt; (ii) H_2O, then CH_3COOH to reach pH 3–4; (iii) 1,4-dioxane/1 M HCl, 4 h, reflux.

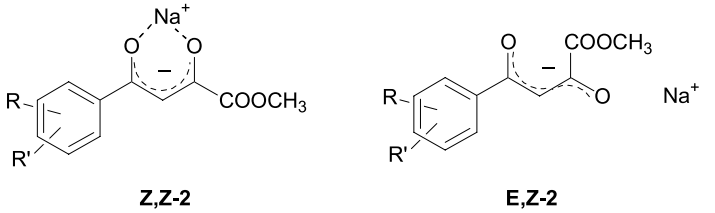
oxalylation of aryl methyl ketones afforded the ketoenol esters **3**, using diethyl or dimethyl oxalate in the presence of NaH (in benzene, toluene or DMF) or NaOEt or NaOMe (in the appropriate alcohol). The reported yields were moderate to good depending on the structure of the aryl methyl ketone and the reaction conditions (base, solvent, reaction temperature and time). Recently, in order to improve this key step, a new procedure using *tert*-butyl methyl oxalate was reported.[16] The reported procedures suffered from a lack of reproducibility, the use of commercially unavailable starting oxalate, long time reaction and high reaction temperature or sometimes tedious extractive work-up.

We herein report a rapid alternative method for the synthesis of ketoenol esters **3** from aryl methyl ketones **1** based on the isolation of sodium ketoenolate esters **2**. Ketoenol acids **4** may be obtained by hydrolysis of **3**[10–16] or more directly from **2** (this work).

2. Results and discussion

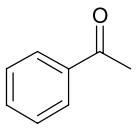
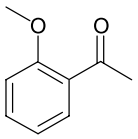
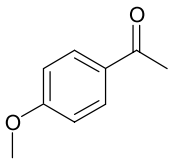
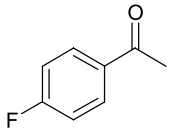
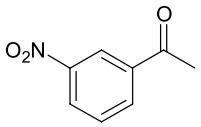
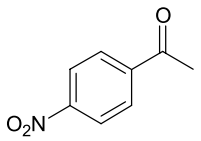
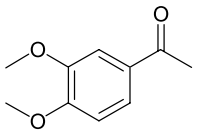
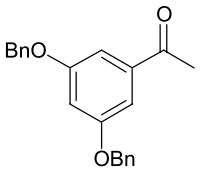
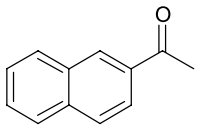
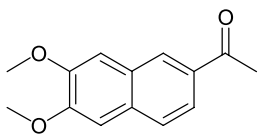
The causes for the absence of a general procedure, the differences in yield and the irreproducibility are mainly due to variable solubility of the starting materials. To overcome this problem, we decided to solubilize the aryl methyl ketone **1** and dimethyl oxalate in dry ether. To this ethereal solution, sodium methoxide in methanol was added. Depending on the aryl methyl ketone used, a precipitate appeared immediately or within half an hour. A reaction time standardized to one night gave satisfactory yields (75–92%) (Table 1). The sodium ketoenolate esters **2(a–j)** were obtained as white to yellowish powders and characterized by ^{1}H NMR spectroscopy (and ^{13}C NMR spectroscopy in the cases of **2a** and **2h**) (Table 2) as a mixture of two species, namely *Z*,*Z* and *E*,*Z* configurations according to Raban and Haritos[17] (Scheme 3). Depending on the ring substitution, the ^{1}H NMR spectra were more or less broadened probably due to a more or less rapid exchange between the two isomers. The sodium ketoenolate esters isomers could be differentiated by the methyl ester signal and the enolic proton signal. *Z*,*Z* Configurations gave a methyl ester signal at 3.63–3.70 ppm and an enolic proton signal at 6.05–6.56 ppm whereas for the *E*,*Z* forms the same signals were at 3.56–3.70 ppm and 5.05–5.57 ppm respectively. The *Z*,*Z*/*E*,*Z* ratio was estimated to be 4:1 except for **2e** (in this case, the characteristic signals of an *E*,*Z* isomer have not been observed on the ^{1}H and ^{13}C NMR spectra). In order to clearly establish the existence of ketoenolate anions and the respective structures of the two configurations, ^{13}C NMR spectra were recorded for **2a** and **2h**. The hydrogen attached to carbon 3 and the carbon 3 of the ketoenolate esters presented strong upfield shifts for the two configurations of **2** (for example: *Z*,*Z*-**2a**: 6.34 and 92.0 ppm, *E*,*Z*-**2a**: 5.31 and 91.9 ppm) versus the chemical shifts in **3** (**3a**: 7.12 and 98.1 ppm) whereas the quaternary carbon of the aromatic ring presented a strong downfield shift (142.2 and 142.4 ppm for *Z*,*Z*-**2a** and *E*,*Z*-**2a**, respectively versus 134.3 ppm for **3a**). These differences were in accordance with previous ^{1}H and ^{13}C NMR studies[18,19] on enolates.

2(a–j) were converted into the corresponding ketoenol esters **3(a–j)** by acidic hydrolysis in moderate to good yields (70–90%). **2(a–c;g–i)** were exhaustively hydrolyzed to give the corresponding ketoenol acids **4(a–c;g–i)** in 45–68% yields by stronger acidic conditions in refluxing dioxane/water mixture. Overall yields (**1→3**) ranged from 58 to 81%. These results suffer the comparison with



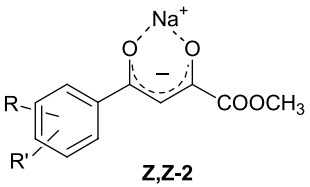
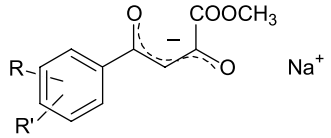
Scheme 3.

Table 1. Preparation of compounds **2**, **3** and **4**

	1	1→2[a] (%)	2→3[a] (%)	1→3	2→4[a] (%)	1→4
a		92	88	81% (lit. 38%[b], 59%[c])	68	63% (lit. 9%[20])
b		88	79	70%	58	51%
c		79	74	58%	50	40%
d		85	90	77% (lit. 100%[d],12%[e])		
e		86	73	63%		
f		80	70	56% (lit. 52%[d], 30%[e])		
g		79	87	69%	45	36%
h		75	82	62% (lit. 85%[f])	65	49% (lit. 64%[20])
i		82	74	61% (lit. 94%[g])	55	45% (lit. 38%[11])
j		86	76	65%		

[a] Yields in isolated pure mixtures of *Z,Z* and *E,Z* forms (**2**) or tautomers (**3** and **4**).
[b] $(CO_2Me)_2$, NaOMe, MeOH, rt, >12 h.[13]
[c] NaH, DMF, $(CO_2Me)_2$, 50 °C, 30 min.[12]
[d] *t*-BuOOCCOOMe, NaOMe, THF–DME (1:1), rt, <2 h.[16]
[e] $(CO_2Me)_2$, NaOMe, THF–DME (1:1), rt, >12 h.[16]
[f] NaH, Toluene, $(CO_2Et)_2$, reflux, 1 h.[20]
[g] NaH, MeOH, Benzene, then **1** and $(CO_2Me)_2$, 12 h.[11]

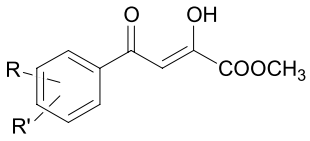
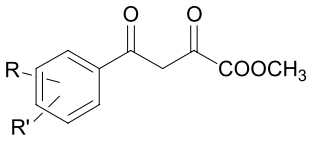
Table 2. Spectroscopic data of compounds **2(a–j)**

Product	 **Z,Z-2**		 **E,Z-2**
	^{1}H NMR (200 MHz, DMSO-d_6) δ, ppm (J, Hz)	^{13}C NMR (50 MHz, DMSO-d_6) δ, ppm (J, Hz)	^{1}H NMR (200 MHz, DMSO-d_6) δ, ppm (J, Hz)
2a	3.68 (s, 3H), 6.34 (s, 1H), 7.40 (m, 3H), 7.79 (br d, 2H)	51.5 (CH_3), 92.0 (CH), 126.5 (2CH), 128.0 (2CH), 129.8 (CH), 142.3 (C), 167.7 (C), 170.3 (C), 185.0 (C)	3.59 (s, 3H), 5.31 (s, 1H), 7.34 (m, 3H), 7.70 (br d, 2H)[a]
2b	3.63 (s, 3H), 3.74 (s, 3H), 6.05 (s, 1H), 6.91–7.00 (m, 2H), 7.28–7.34 (m, 2H)	51.5 (CH_3), 55.4 (CH_3), 97.6 (CH), 111.7 (CH), 120.0 (CH), 128.6 (CH), 129.7 (CH), 133.8 (C), 156.2 (C), 167.8 (C), 169.1 (C), 187.2 (C)	3.63 (s, 3H), 3.74 (s, 3H), 5.05 (br s, 1H), 6.91–7.00 (m, 2H), 7.28–7.34 (m, 2H)
2c	3.66 (s, 3H), 3.78 (s, 3H), 6.33 (s, 1H), 6.92 (d, 2H, ^3J=8.1), 7.77 (d, 2H, ^3J=8.1)	51.6 (CH_3), 55.2 (CH_3), 91.6 (CH), 113.3 (2CH), 128.4 (2CH), 134.5 (C), 160.9 (C), 167.9 (C), 169.5 (C), 184.8 (C)	3.56 (s, 3H), 3.78 (s, 3H), 5.28 (s, 1H), 6.88 (d, 2H, ^3J=7.6), 7.66 (d, 2H, ^3J=7.6)
2d	3.67 (s, 3H), 6.29 (s, 1H), 7.19 (br dd, 2H, $^3J_{HH}$=8.3, $^3J_{HF}$=9.0), 7.83 (dd, 2H, $^3J_{HH}$=8.3, $^4J_{HF}$=5.9)	51.7 (CH_3), 91.9 (CH), 114.8 (2CH, $^2J_{CF}$=22.0), 129.0 (2CH, $^3J_{CF}$=9.2), 138.5 (C, $^4J_{CF}$=3.0), 163.3 (C, $^1J_{CF}$=247.8), 167.6 (C), 170.2 (C), 184.2 (C)	3.58 (s, 3H), 5.28 (s, 1H), 7.14 (m, 2H), 7.77 (m, 2H)
2e	3.67 (s, 3H), 6.20 (br s, 1H), 7.68 (br t, 1H, ^3J=7.9), 8.19–8.26 (m, 2H), 8.53 (br s, 1H)	51.6 (CH_3), 92.1 (CH), 121.0 (CH), 124.5 (CH), 129.9 (CH), 132.8 (CH), 143.2 (C), 147.9 (C), 167.3 (C), 172.9 (C), 181.7 (C)	
2f	3.68 (s, 3H), 6.33 (s, 1H), 7.98 (d, 2H, ^3J=8.3), 8.23 (d, 2H, ^3J=8.3)	51.6 (CH_3), 92.5 (CH), 123.4 (2CH), 127.7 (2CH), 148.0 (C), 148.1 (C), 167.1 (C), 171.8 (C), 182.1 (C)	3.60 (s, 3H), 5.36 (s, 1H), 7.93 (d, 2H, ^3J=8.3), 8.17 (d, 2H, ^3J=8.3)
2g	3.66 (s, 3H), 3.77 (br s, 6H), 6.36 (br s, 1H), 6.94 (br d, 1H), 7.39 (m, 2H)	51.5 (CH_3), 55.3 (CH_3), 55.5 (CH_3), 91.6 (CH), 109.9 (CH), 110.7 (CH), 119.7 (CH), 134.7 (C), 148.2 (C), 150.6 (C), 167.8 (C), 169.8 (C), 184.6 (C)	3.66 (s, 3H), 3.77 (br s, 6H), 5.30 (br s, 1H), 6.94 (br d, 1H), 7.39 (m, 2H)
2h	3.66 (s, 3H), 5.10 (s, 4H), 6.22 (s, 1H), 6.73 (br s, 1H), 6.98 (br s, 2H), 7.32–7.43 (m, 10H)	51.4 (CH_3), 69.3 ($2CH_2$), 91.9 (CH), 103.4 (CH), 105.6 (2CH), 127.6 (4CH), 127.8 (2CH), 128.40 (4CH), 137.0 (2C), 144.8 (C), 159.2 (2C), 167.6 (C), 170.8 (C), 184.2 (C)	3.57 (s, 3H), 5.10 (s, 4H), 5.24 (s, 1H), 6.63 (br s, 1H), 6.95 (br s, 1H), 7.32–7.43 (m, 10H)[b]
2i	3.72 (s, 3H), 6.60 (s, 1H), 7.52 (br s, 2H), 7.91 (m, 4H), 8.39 (br s, 1H)	51.8 (CH_3), 92.6 (CH), 124.5 (CH), 126.4 (2CH), 127.0 (CH), 127.5 (CH), 127.6 (CH), 129.0 (CH), 132.6 (C), 133.9 (C), 139.6 (C), 167.8 (C), 170.4 (C), 185.4 (C)	3.72 (s, 3H), 5.57 (br s, 1H), 7.52 (br s, 2H), 7.91 (m, 4H), 8.39 (br s, 1H)
2j	3.69 (s, 3H), 3.88 (br s, 6H), 6.50 (br s, 1H), 7.29 (br s, 1H), 7.45 (br s, 1H), 7.73–7.80 (m, 2H), 8.23 (br s, 1H)	51.5 (CH_3), 55.4 (CH_3), 55.6 (CH_3), 92.1 (CH), 106.1 (CH), 107.5 (CH), 122.5 (CH), 124.9 (CH), 125.8 (CH), 128.2 (C), 129.9 (C), 137.7 (C), 149.4 (C), 150.1 (C), 167.9 (C), 170.2 (C), 185.3 (C)	3.60 (s, 3H), 3.88 (br s, 6H), 5.46 (br s, 1H), 7.29 (br s, 1H), 7.45 (br s, 1H), 7.73–7.80 (m, 2H), 8.12 (br s, 1H)

[a] ^{13}C NMR (50 MHz, DMSO-d_6): δ=50.3 (CH_3), 91.9 (CH), 126.4 (2CH), 127.6 (2CH), 129.0 (CH), 142.4 (C), 170.4 (C), 180.2 (C), 182.7 (C).

[b] ^{13}C NMR (50 MHz, DMSO-d_6): δ=50.3 (CH_3), 69.2 ($2CH_2$), 92.1 (CH), 103.2 (CH), 105.3 (2CH), 127.5 (4CH), 127.7 (2CH), 128.38 (4CH), 137.2 (2C), 145.1 (C), 158.9 (2C), 170.3 (C), 180.4 (C), 182.0 (C).

Table 3. Spectroscopic data of compounds **3(a–j)**

Product	Ketoenol/diketo ratio[a]	Ketoenol-form		Diketo-form
				
		^{1}H NMR (200 MHz, DMSO-d_6) δ, ppm (J, Hz)	^{13}C NMR (50 MHz, DMSO-d_6) δ, ppm (J, Hz)	^{1}H NMR (200 MHz, DMSO-d_6) Detectable signals δ, ppm (J, Hz)
3a	90:10	3.86 (s, 3H), 7.12 (s, 1H), 7.57 (br t, 2H, ^3J=7.1), 7.70 (br t, 1H, ^3J=7.1), 8.06 (br d, 2H, ^3J=7.1)	53.0 (CH_3), 98.1 (CH), 127.9 (2CH), 129.1 (2CH), 134.1 (CH), 134.3 (C), 162.0 (C), 168.7 (C), 190.2 (C)	3.78 (s, 3H), 4.62 (s, 2H), 7.99 (br d, 2H)
3b	84:16	3.82 (s, 3H), 3.89 (s, 3H), 7.06 (br dd, 1H, ^3J=7.3, ^3J=6.7), 7.15 (s, 1H), 7.17 (br d, 1H, ^3J=8.8), 7.58 (1H, br dd, ^3J=8.8, ^3J=6.7), 7.77 (1H, br d, ^3J=7.3)	52.9 (CH_3), 55.9 (CH_3), 102.8 (CH), 112.7 (CH), 120.7 (CH), 123.6 (C), 130.0 (CH), 135.1 (CH), 158.9 (C), 162.3 (C), 168.4 (C), 189.4 (C)	4.38 (s, 2H), 7.73 (br d, 1H)
3c	96:4	3.84 (s, 3H), 3.85 (s, 3H), 7.05 (s, 1H), 7.07 (d, 2H, ^3J=8.9), 8.05 (d, 2H, ^3J=8.9)	52.9 (CH_3), 55.7 (CH_3), 97.7 (CH), 114.5 (2CH), 127.2 (C), 130.5 (2CH), 162.5 (C), 164.1 (C), 167.2 (C), 189.9 (C)	4.53 (s, 2H)
3d	91:9	3.85 (s, 3H), 7.10 (s, 1H), 7.38 (br dd, 2H, $^3J_{HH}$=8.6, $^3J_{HF}$=9.0), 8.15 (dd, 2H, $^3J_{HH}$=8.6, $^4J_{HF}$=5.6)	53.1 (CH_3), 98.2 (CH), 116.2 (2CH, $^2J_{CF}$=22.0), 131.1 (2CH, $^3J_{CF}$=9.8), 131.5 (C), 162.0 (C), 165.6 (C, $^1J_{CF}$=253.3), 167.8 (C), 189.4 (C)	3.77 (s, 3H), 4.60 (s, 2H), 7.38 (br dd, 2H, $^3J_{HH}$=8.6, $^3J_{HF}$=9.0), 8.05 (dd, 2H, $^3J_{HH}$=8.6, $^4J_{HF}$=5.6)
3e	90:10	3.86 (s, 3H), 7.14 (s, 1H), 7.82 (m, 1H), 8.44–8.47 (m, 2H), 8.64 (br s, 1H)	53.1 (CH_3), 98.6 (CH), 122.1 (CH), 127.9 (CH), 130.8 (CH), 134.0 (CH), 135.9 (C), 148.2 (C), 161.9 (C), 168.7 (C), 187.4 (C)	3.79 (s, 3H), 4.70 (s, 2H)
3f	93:7	3.86 (s, 3H), 7.12 (s, 1H), 8.27 (d, 2H, ^3J=9.0), 8.34 (d, 2H, ^3J=9.0)	53.2 (CH_3), 98.8 (CH), 124.0 (2CH), 129.2 (2CH), 139.5 (C), 150.2 (C), 161.9 (C), 170.2 (C), 186.5 (C)	3.78 (s, 3H), 4.68 (s, 2H), 8.20 (d, 2H, ^3J=9.0), 8.34 (d, 2H, ^3J=9.0)
3g	93:7	3.84 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 7.10 (d, 1H, ^3J=8.6), 7.11 (s, 1H), 7.52 (d, 1H, ^4J=2.2), 7.77 (dd, 1H, ^3J=8.6, ^4J=2.2)	53.0 (CH_3), 55.6 (CH_3), 55.9 (CH_3), 98.1 (CH), 110.0 (CH), 111.3 (CH), 123.2 (CH), 127.1 (C), 148.9 (C), 154.2 (C), 162.3 (C), 166.7 (C), 190.5 (C)	3.77 (s, 3H), 3.81 (s, 3H), 4.56 (s, 2H), 7.08 (d, 1H, ^3J=8.7), 7.42 (br s, 1H), 7.63 (br d, 1H, ^3J=8.7)
3h	Diketo-form undetected	3.79 (s, 3H), 5.16 (br s, 4H), 6.93 (br s, 2H), 7.20 (br s, 2H), 7.37–7.44 (m, 10H)	52.5 (CH_3), 69.6 ($2CH_2$), 96.8 (CH), 106.4 (3CH), 127.7 (4CH), 127.9 (2CH), 128.5 (4CH), 136.7 (2C), 138.8 (C), 159.7 (2C), 163.7 (C), 169.5 (C), 188.3 (C)	
3i	97:3	3.86 (s, 3H), 7.24 (s, 1H), 7.60–7.66 (m, 2H), 7.95–8.00 (m, 3H), 8.13 (d, 1H, ^3J=7.6), 8.75 (br s, 1H)	53.0 (CH_3), 98.3 (CH), 123.0 (CH), 127.1 (CH), 127.7 (CH), 128.7 (CH), 129.1 (CH), 129.8 (CH), 130.1 (CH), 131.8 (C), 132.2 (C), 135.4 (C), 162.2 (C), 168.1 (C), 190.3 (C)	4.74 (s, 2H), 8.62 (br s, 1H)
3j	96:4	3.87 (s, 3H), 3.90 (s, 3H), 3.92 (s, 3H), 7.24 (s, 1H), 7.40 (s, 1H), 7.58 (s, 1H), 7.87 (m, 2H), 8.64 (br s, 1H)	53.0 (CH_3), 55.5 (CH_3), 55.7 (CH_3), 98.1 (CH), 106.4 (CH), 108.1 (CH), 121.5 (CH), 127.0 (CH), 128.1 (C), 128.5 (CH), 129.9 (C), 132.3 (C), 149.9 (C), 151.9 (C), 162.3 (C), 167.6 (C), 190.7 (C)	4.66 (s, 2H), 8.51 (br s, 1H)

[a] The ratios were calculated from the ethylenic proton signal of the ketoenol isomer and the methylenic protons signal of the diketo isomer in DMSO-d_6.

Table 4. Physical, analytical and mass spectroscopic data for compounds **3(b–c)**, **3(e–h)** and **3j**[a]

Product	State	Mp (°C)	Elemental analyses	MS (EI)
3b	Yellow powder	75–76	Anal. calcd for $C_{12}H_{12}O_5$ (236.22): C, 61.01; H, 5.12. Found: C, 61.28; H, 5.22	*m/z* (%)=236 ([M^+], 1), 177 (56), 135 (100), 77 (19)
3c	Yellow powder	92–93	Anal. calcd for $C_{12}H_{12}O_5$ (236.22): C, 61.01; H, 5.12. Found: C, 61.35; H, 5.06	*m/z* (%)=236 ([M^+], 16), 178 (12), 177 (100), 135 (33), 109 (38), 94 (14), 77 (12), 69 (21)
3e	Beige powder	112–113	Anal. calcd for $C_{11}H_9NO_6$ (251.20): C, 52.60; H, 3.61; N, 5.58. Found: C, 52.31; H, 3.72; N, 5.35	*m/z* (%)=251 ([M^+], 2), 193 (10), 192 (100), 150 (18), 105 (11), 69 (11)
3f	White powder	161–162	Anal. calcd for $C_{11}H_9NO_6$ (251.20): C, 52.60; H, 3.61; N, 5.58. Found: C, 52.25; H, 3.68; N, 5.42	*m/z* (%)=251 ([M^+], 2), 193 (11), 192 (100), 150 (19), 146 (13), 105 (14), 69 (19)
3g	Yellow powder	150–151	Anal. calcd for $C_{13}H_{14}O_6$ (266.25): C, 58.64; H, 5.30. Found: C, 58.96; H, 5.22	*m/z* (%)=266 ([M^+], 56), 208 (12), 207 (100), 165 (24), 139 (87), 124 (69), 69 (14)
3h	Yellow powder	121–123	Anal. calcd for $C_{25}H_{22}O_6$ (418.45): C, 71.76; H, 5.30. Found: C, 71.95; H, 5.35	*m/z* (%)=418 ([M^+], 29), 359 (9), 327 (16), 227 (10), 181 (48), 180 (34), 91 (100)
3j	Yellow powder	170–172	Anal. calcd for $C_{17}H_{16}O_6$ (316.31): C, 64.55; H, 5.10. Found: C, 64.24; H, 5.15	*m/z* (%)=317 (11), 316 ([M^+], 64), 258 (19), 257 (98), 230 (12), 215 (46), 190 (14), 189 (100), 174 (78), 172 (11)

[a] Known products: **3a**, white powder, mp 57–58 °C (lit.[13] mp 56–57 °C); **3d**, white powder, mp 124–125 °C (lit.[13] mp 125 °C); **3i**, white powder, mp 104–105 °C (lit.[11] mp 104–106 °C).

previous articles except for the yield of **1d→3d** that was reported to reach 100% after column chromatography purification.[16] L-708,906, **4h** was obtained in 64% yield in a recent patent,[20] whereas its unsubstituted parent molecule **4a** was obtained in the same report in a poor 9% yield. No doubt the procedure for the synthesis of L-708,906 was optimized in comparison with that of **4a**. A 94% yield was also reported for the synthesis of **3i** but the yield of its conversion into **4i** dropped to 38%.[11] Since our overall yields in **4i** from **1i** are similar, we may have some doubt about the purity of **3i** in the cited paper. Physical data of ketoenol esters **3** are reported in Tables 3 and 4 and physical data of DKAs **4** in Table 5.

As a conclusion, we reported in this paper, a very simple and efficient procedure for the synthesis of ketoenol esters **3** and acids **4** that allows variable substitution on the aromatic ring. This new protocol involves the isolation of the unpreviously reported sodium keto enolate esters **2** as a key step that may be hydrolyzed under soft conditions into **3** or more hardly treated to give **4**. The yields in **2** are quite good and the conversions into **3** or **4** are acceptable. Due to its remarkable simplicity, this new procedure may be of great interest for the rapid synthesis of a wide range of new DKAs.

3. Experimental

All solvents were of commercial quality used from freshly opened containers and were dried and purified by conventional methods. Aryl methyl ketones **1** were purchased from Aldrich-Chimie (St Quentin-Fallavier, France) except for **1j**. 1-(6,7-dimethoxynaphthalen-2-yl)-ethanone **1j** was prepared in two steps from 2,3-dimethoxynaphthalene according to a known procedure.[23]

Mps were determined on a Reichert Thermopan apparatus, equipped with a microscope and are uncorrected. NMR spectra were obtained on a AC 200 Bruker spectrometer in DMSO-d_6 with TMS as internal reference. Mass spectra were recorded on a Thermo-Finnigan PolarisQ mass spectrometer (70 eV, Electronic Impact). Elemental analyses were performed by CNRS laboratories (Vernaison).

3.1. Synthesis of sodium ketoenolate ester 2. General procedure

Sodium (0.28 g, 12 mmol) was added slowly in methanol (6 mL) at −5 °C to give a 2 M solution of sodium methoxide. Arylmethyl ketone **1** (10 mmol) and dimethyl oxalate (1.18 g, 10 mmol) were dissolved in dried diethyl ether (10 mL) and the freshly prepared solution of sodium methoxide was slowly added. The mixture was stirred overnight, the solid was filtered off, washed with methanol, diethyl ether and dried. Sodium ketoenolate esters **2** were obtained in yields ranging from 75 to 92%.

3.2. Synthesis of ketoenol ester 3. General procedure

Sodium ketoenolate ester **2** (1 g) was dissolved in water (about 100 mL) at rt for 1 h. Then the solution was acidified by adding acetic acid to reach pH 3–4 and kept at 0 °C for 1 h. The precipitate was filtered off, washed with water and dried. Ketoenol esters **3** were obtained in yields ranging from 70 to 90%.

3.3. Synthesis of ketoenol acid 4. General procedure

Sodium ketoenolate ester **2** (1 g) was partially dissolved in 1,4-dioxane (20–30 mL) and 1 M HCl (100 mL) was added. The mixture was refluxed during 6 h. Removal of the solvent under reduced pressure gave a solid, which was washed with water, CH_2Cl_2 and dried. The product was recrystallized from diethyl ether (**4a**), toluene/ethyl acetate (**4b–c**) or ethyl acetate (**4g–i**). Ketoenol acids **4** were obtained as yellow solids in yields ranging from 45 to 68%.

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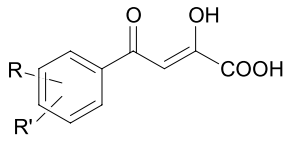
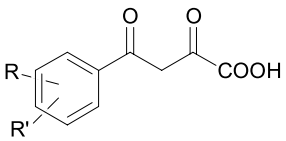
Table 5. Physical and spectroscopic data of compounds **4(a–c)** and **4(g–i)**

Product	Mp (°C)	Ketoenol/diketo ratio[a]			
			Ketoenol-form		Diketo-form
			^{1}H NMR (200 MHz, DMSO-d_6) δ, ppm (J, Hz)	^{13}C NMR (50 MHz, DMSO-d_6) δ, ppm	^{1}H NMR (200 MHz, DMSO-d_6), detectable signals δ, ppm (J, Hz)
4a	154–157 (lit.[15] 155–158)	91:9	7.09 (s, 1H), 7.55 (br dd, 2H, ^3J=7.3, ^3J=6.7), 7.68 (br t, 1H, ^3J=6.7), 8.04 (br d, 2H, ^3J=7.3)	97.8 (CH), 127.8 (2CH), 129.1 (2CH), 134.0 (CH), 134.6 (C), 163.1 (C), 170.1 (C), 190.4 (C)	4.56 (s, 2H), 7.96 (br d, 2H, ^3J=7.4)
4b	155–157[b]	83:17	3.89 (s, 3H), 7.07 (br dd, 1H, ^3J=7.3, ^3J=6.6), 7.17 (s, 1H), 7.19 (br d, 1H, ^3J=8.3), 7.59 (br dd, 1H, ^3J=8.3, ^3J=6.6), 7.78 (br d, 1H, ^3J=7.3)	56.1 (CH_3), 102.8 (CH), 112.8 (CH), 120.9 (CH), 124.0 (C), 130.1 (CH), 135.1 (CH), 158.9 (C), 163.4 (C), 169.8 (C), 189.9 (C)	3.81 (s, 3H), 4.34 (s, 2H), 7.72 (br d, 1H)
4c	157–158 (lit.[21] 160–162)	89:11	3.84 (s, 3H), 6.90 (s, 1H), 7.06 (d, 2H, ^3J=8.3), 8.01 (d, 2H, ^3J=8.3)	55.7 (CH_3), 97.4 (CH), 114.4 (2CH), 127.5 (C), 130.2 (2CH), 162.5 (C), 163.6 (C), 171.1 (C), 188.7 (C)	4.41 (s, 2H), 7.93 (d, 2H, ^3J=8.4)
4g	188–189 (lit.[22] 179–180 dec.)	90:10	3.84 (s, 3H), 3.86 (s, 3H), 7.08 (s, 1H), 7.10 (d, 1H, ^3J=8.6), 7.53 (d, 1H, ^4J=1.5), 7.76 (dd, 1H, ^3J=8.6, ^4J=1.5)	55.6 (CH_3), 55.9 (CH_3), 97.8 (CH), 109.9 (CH), 111.3 (CH), 123.0 (CH), 127.3 (C), 148.9 (C), 154.0 (C), 163.4 (C), 168.3 (C), 190.4 (C)	3.81 (s, 3H), 4.50 (s, 2H), 7.43 (br s, 1H), 7.63 (br d, 1H, ^3J=8.8)
4h	171–173 (lit.[15] 170–172)	90:10	5.18 (s, 4H), 6.99 (br s, 1H), 7.09 (s, 1H), 7.26 (br s, 2H), 7.31–7.47 (m, 10H)	69.7 ($2CH_2$), 98.2 (CH), 106.6 (2CH), 107.6 (CH), 127.8 (4CH), 128.0 (2CH), 128.5 (4CH), 136.6 (2C), 136.8 (C), 159.8 (2C), 163.2 (C), 170.2 (C), 190.0 (C)	4.54 (s, 2H), 7.20 (br s, 2H)
4i	174–175 (lit.[11] 173–175)	93:7	7.29 (s, 1H), 7.60–7.70 (m, 2H), 7.98–8.05 (m, 3H), 8.17 (d, 1H, ^3J=8.3), 8.81 (br s, 1H)	98.2 (CH), 123.1 (CH), 127.1 (CH), 127.7 (CH), 128.8 (CH), 129.1 (CH), 129.8 (CH), 130.1 (CH), 132.0 (C), 132.3 (C), 135.4 (C), 163.2 (C), 169.6 (C), 190.6 (C)	4.70 (s, 2H), 8.71 (br s, 1H)

[a] The ratios were calculated from the ethylenic proton signal of the ketoenol isomer and the methylenic protons signal of the diketo isomer in DMSO-d_6.
[b] Anal. calcd for $C_{11}H_{10}O_5$ (222.20): C, 59.46; H, 4.54. Found: C, 59.24; H, 4.63. MS (EI): m/z (%)=222 ([M^+], 2), 192 (11), 177 (70), 149 (10), 135 (100), 79 (12), 77 (27).

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