# Annelation of Baylis–Hillman derivatives: synthesis of highly functionalised tetrahydronaphthalenes

**Asma J'mour and Farhat Rezgui***

*Laboratoire de Chimie Organique, Faculté des Sciences de Tunis, Campus Universitaire 2092 Tunis, Tunisia*

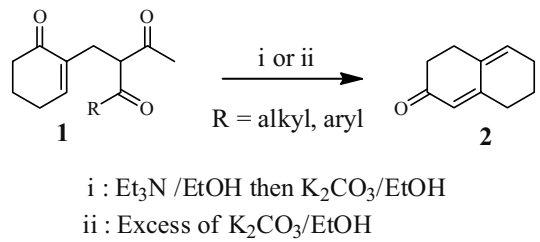
PTSA-promoted Robinson annelation of α-(3-oxobutyl)cyclohex-2-en-1-one derivatives in refluxing toluene, affords efficiently in a *one pot* process a variety of hydroxytetrahydronaphthyl carbonyl compounds in good yields. Further highly regioselective electrophilic bromination of these intermediates gave the corresponding bromide derivatives in 92–97% yield.

**Keywords:** Baylis–Hillman alcohols, tetrahydronaphthyl carbonyl compounds, Robinson annelation, electrophilic bromination, regioselectivity

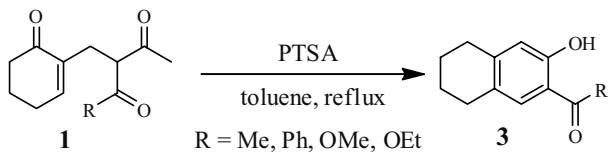
Hydroxyaryl carbonyl compounds are useful intermediates in organic chemistry and for the preparation of biologically active targets.[1] These versatile derivatives are commonly prepared from the Fries rearrangement of aryl esters in the presence of Lewis acids such as aluminium(III) chloride,[2,3] titanium(III) chloride[4-6] or zirconium(III) chloride.[7] Unfortunately, in many cases, this protocol furnished a mixture of regioisomers together with side-products.[8-10] Therefore, intense efforts have been undertaken either to improve the regioselectivity of the Fries rearrangement[11] or to develop new approaches towards this important class of compounds.[12]

Furthermore, in our previous papers,[13,14] starting from α-(3-oxobutyl)cyclohex-2-en-1-one derivatives **1** in basic conditions, we have described two synthetic routes (i) or (ii) to a new series of bicyclic dienones **2** (Scheme 1).

In continuation of our study on the intramolecular aldol condensation of multifunctional derivatives **1**, we report here their use as intermediates in a simple synthetic method for hydroxy-5,6,7,8-tetrahydronaphthyl carbonyl compounds (THN) **3**. We also disclosed a general procedure for highly regioselective electrophilic bromination of these aryl carbonyl derivatives **3**, yielding a new series of potential intermediates **4** for AMP deaminase inhibitors.[15,16]




**Scheme 1** Annelation of compounds **1** in basic conditions.




**Scheme 2** PTSA-catalysed annelation of 1,5-diketones **1.**

## Results and discussion

During our investigation on Robinson annelation of 1,5-dicarbonyl compounds **1** in acidic conditions, we first found that intramolecular aldol reaction of compound **1a** and a catalytic amount (0.1 equiv.) of PTSA (*p*-toluene sulfonic acid) proceeded rapidly in refluxing toluene, affording cleanly in a straightforward process the single hydroxyaryl ketone **3a** in 90% yield (Scheme 2).

Concerning the mechanistic aspect of this reaction, we assume that the present protocol proceeded in a three-step reaction sequence including (i) Robinson annelation-crotonisation giving $\mathbf{I_1}$ that underwent further tautomerisation (ii) and (iii) aromatisation, affording hydroxytetrahydronaphthyl ketone **3a** in good yield (Scheme 3).

The spectroscopic data of **3a** are in agreement with those of literature.[12,17]

Using the optimal cyclisation conditions (0.1 equiv of PTSA in refuxing toluene) previously etablished for the preparation of **3a**, we then examined the access to its analogous derivatives **3b–d**. During our study, we similarly observed that a one pot three-step reaction proceeded smoothly to give regioselectively and in good yields the corresponding THN **3b–d** (Scheme 2, Table 1).

Note that in contrast to our previous communications on $K_2CO_3$-promoted intramolecular cyclisation of compounds **1** into bicyclic dienones **2**[13,14] (Scheme 1)**,** the present procedure describes their acidic Robinson annelation into functionalised THN **3,** however, without further deacylation reactions.

In the literature,[15,16] bromohydroxytetrahydronaphthyl carbonyl compounds **3** are described as potential precursors, *via* their corresponding homobenzylic bromide derivatives **5**, for potent inhibitors **6** of adenosine deaminase (Scheme 4).

Treatment of compound **3d** with bromine in acetic acid, we first prepared through a highly regioselective electrophilic bromination, the single bromohydroxynaphthyl ester **4d** in excellent yield (Scheme 5, Table 2).

The crystalline structure of compound **4d**,[18,19] confirmed the preferential attack at the *ortho* position to the hydroxyl group of **3d**. This interesting regioselectivity is in agreement with the fact that the hydroxyl group is a strongly activating *o*- (exclusively available here), *p*-directing substituent.

This simple, efficient procedure (*e.g.* $Br_2$ in AcOH) has been also applied to perform the electrophilic bromination of hydroxytetrahydronahthyl carbonyl compounds **3a–c**. As seen in Table 2, we have successfully and cleanly prepared the corresponding bromide derivatives **4a–c** in 92–97% yield.

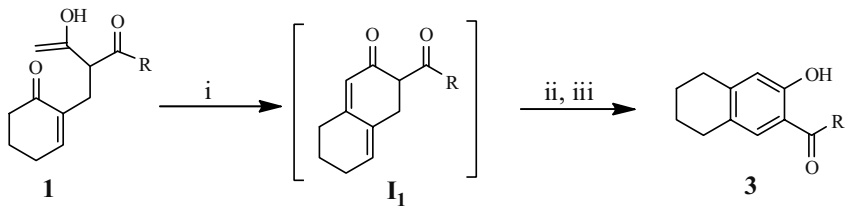
**Table 1** PTSA-catalysed annelation of 1,5-diketones **1**

| **3** | **a** | **b** | **c** | **d** |
|---|---|---|---|---|
| R | Me | Ph | OMe | OEt |
| Yield (%) | 90 | 91 | 75 | 82 |

**Table 2** Electrophilic bromination of compounds **3**

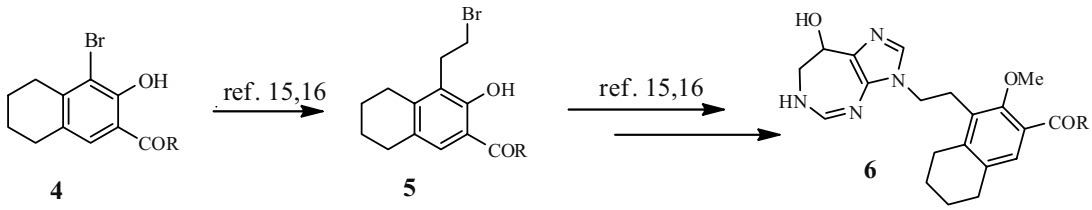
| **4** | **a** | **b** | **c** | **d** |
|---|---|---|---|---|
| R | $CH_3$ | Ph | OMe | OEt |
| Yield/% | 97 | 92 | 92 | 96 |

* Correspondent. E-mail: rez_far@yahoo.fr

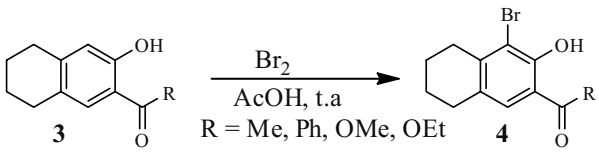



i: Robinson annelation-crotonisation, ii: tautomerisation, iii: aromatisation

**Scheme 3** A plausible reaction mechanism of PTSA-catalysed annelation of compound **1**.




**Scheme 4** Bromide derivatives **4** as useful precursors for inhibitors 6 of adenosine deaminase.




**Scheme 5** Electrophilic bromination of compounds **3**.

## Conclusions

The present work describes PTSA-promoted Robinson annelation of 2-(3-oxobutyl)cyclohex-2-en-1-one derivatives **1** in refluxing toluene to give, *via* an efficient *tandem* reactions sequence, a variety of THN **3** which were further subjected to electrophilic bromination conditions in acetic acid, to afford in good yields and in high regioselectivity the corresponding bromohydroxynaphthyl derivatives **4** as useful intermediates for the synthesis of AMP deaminase inhibitors.

## Experimental

*General*

$^1$H NMR spectra were recorded in $CDCl_3$ solutions at 300 MHz with tetramethylsilane as internal reference. $^{13}$C NMR spectra were recorded at 75 MHz with $CDCl_3$ as internal reference. Chemical shifts are given in ppm (δ) and coupling constants *J* are reported in Hz. IR spectra were obtained on a Perkin Elmer Paragon 1000 PC IR spectrometer. Mass spectra were measured on a Hewlett-Packard 5890 spectrometer at 70 eV (EI). Column chromatography was performed using silica gel 60 (70–230 mesh).

*Typical procedure for the preparation of tetrahydronaphthyl carbonyl compounds* **3a–d**

A mixture of 2-(3-oxobutyl)cyclohex-2-en-1-one **1** (2 mmol),[13] a catalytic amount (0.1 equiv.) of PTSA and 5 mL of toluene, was refluxed for 2 h. The reaction mixture was diluted with dichloromethane (20 mL) and washed successively with saturated aqueous $NaHCO_3$ and with brine. The organic layer was dried over $Na_2SO_4$. After evaporation of the solvents, the product was purified by a column chromatography (ether/petroleum ether: 5/95).

*1-(3-Hydroxy-5,6,7,8-tetrahydro-2-naphthyl)ethanone* **(3a):** A known compound.[17] M.p. 71 °C (lit.[17]: m.p. 71–72 °C); yield (90%). IR ($CHCl_3$): 3673, 1639 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): δ 11.98 (s, 1H), 7.40 (s, 1H), 6.67 (s, 1H), 2.78–2.72 (m, 4H), 2.63 (s, 3H), 1.81–1.74 (m, 4H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 203.9, 159.8, 147.4, 130.8, 127.8, 117.9, 117.5, 29.9, 28.5, 26.5, 23.1, 22.6. MS (EI, 70 eV); *m/z* (%): 147 (15), 175 (100), 190 ($M^+$, 43). HRMS Calcd for $C_{12}H_{14}O_2$ 190.0994. Found 190.0994.

*1-(3-Hydroxy-5,6,7,8-tetrahydro-2-naphthyl)phenylmethanone* **(3b)**: Yellow oil; yield (91%). IR ($CHCl_3$): 3684, 1632 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): δ 11.81 (s, 1H), 7.66–7.45 (m, 5H), 7.25 (s, 1H), 6.76 (s, 1H), 2.77–2.75 (m, 2H), 2.63–2.61 (m, 2H), 1.77–1.73 (m, 4H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 201.1, 160.7, 147.4, 138.2, 133.6, 131.5, 129.0, 128.2, 127.7, 117.6, 117.3, 30.0, 28.5, 23.1, 22.6. HRMS Calcd for $C_{17}H_{16}O_2$ 252.1150. Found 252.1150.

*Methyl-3-hydroxy-5,6,7,8-tetrahydronaphthalene-2-carboxylate* **(3c):** Yellow oil; yield (75%). IR ($CHCl_3$): 3219, 1675 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): δ 10.41 (s, 1H), 7.51 (s, 1H), 6.67 (s, 1H), 3.91 (s, 3H), 2.74–2.68 (m, 4H), 1.77–1.76 (m, 4H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 170.5, 158.9, 146.3, 129.8, 128.1, 116.9, 110.0, 52.0, 29.8, 28.4, 23.2, 22.7. HRMS Calcd for $C_{12}H_{14}O_3$ 206.0943. Found 206.0942.

*Ethyl-3-hydroxy-5,6,7,8-tetrahydronaphthalene-2-carboxylate* **(3d):** Yellow oil; yield (82%). IR ($CHCl_3$): 3674, 3532, 3211, 1671 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): δ 10.52 (s, 1H), 7.51 (s, 1H), 6.65 (s, 1H), 4.36 (q, 2H, *J* = 6.73 Hz), 2.77–2.66 (m, 4H), 1.79–1.74 (m, 4H), 1.40 (t, 3H, *J* = 6.39 Hz). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 170.1, 159.1, 146.0, 129.8, 128.0, 116.8, 110.3, 61.0, 30.0, 28.4, 23.2, 22.7, 14.2. MS (EI, 70 eV); *m/z* (%): 117 (17), 146 (11), 174 (100), 220 ($M^+$, 31). HRMS Calcd for $C_{13}H_{16}O_3$ 220.1099. Found 220.1099.

*Typical procedure for the preparation of* **4a–d**

To a solution of tetrahydronaphthyl carbonyl compounds (2 mmol) **3** in 2 mL of acetic acid, was added dropwise a solution of bromine (2 mmol) in 2 mL of acetic acid under stirring at room temperature. After additional 2 h, the resulting mixture was diluted with water and extracted with dichloromethane. The organic layer was washed with water until neutrality. After usual work up, the residue was purified by a column chromatography (petroleum ether).

*1-(4-Bromo-3-hydroxy-5,6,7,8-tetrahydro-2-naphthyl)ethanone* **(4a):** M.p. 142 °C, yield (97%). $^1$H NMR (300 MHz, $CDCl_3$): δ 12.78 (s, 1H), 7.38 (s, 1H), 2.78–2.70 (m, 4H), 2.67 (s, 3H), 1.83–1.72 (m, 4H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 203.8, 156.4, 146.2, 129.5, 129.3, 117.9, 114.3, 31.3, 29.4, 26.5, 22.7, 22.5. MS (EI, 70 eV); *m/z* (%): 115 (26), 117 (12), 145 (16), 146 (27), 253 (100), 255 (97), 268 ($M^+$, 66). HRMS Calcd for $C_{12}H_{13}BrO_2$ 268.0099. Found 268.0100.

*1-(4-Bromo-3-hydroxy-5,6,7,8-tetrahydro-2-naphthyl)(phenyl) methanone* **(4b):** M.p. 121 °C; yield (92%). $^1$H NMR (300 MHz, $CDCl_3$): δ 12.49 (s, 1H), 7.58–7.38 (m, 5H), 7.18 (s, 1H), 2.75–2.71 (m, 2H), 2.59–2.55 (m, 2H), 1.77–1.59 (m, 4H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 200.8, 157.2, 146.2, 137.6, 132.3, 132.0, 129.1, 128.4, 128.3, 117.4, 114.5, 31.3, 29.6, 22.7, 22.6. MS (EI, 70 eV); *m/z* (%): 77 (79), 105 (80), 253 (58), 255 (53), 329 (82), 330 ($M^+$, 96), 331 ($MH^+$, 100).

*Methyl-4-bromo-3-hydroxy-5,6,7,8-tetrahydronaphthalene-2-carboxylate* **(4c):** M.p. 86 °C; yield (92%). $^1$H NMR (300 MHz, $CDCl_3$): δ 11.13 (s, 1H), 7.42 (s, 1H), 3.85 (s, 3H), 2.70–2.59 (m, 4H), 1.75–1.60 (m, 4H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 170.2, 155.6, 145.2, 129.6, 128.6, 113.6, 110.4, 52.5, 31.2, 29.3, 22.7, 22.5. MS (EI, 70 eV); *m/z* (%): 115 (20), 117 (12), 173 (18), 252 (100), 254 (98), 284 ($M^+$, 22). HRMS Calcd for $C_{12}H_{13}BrO_3$ 284.0048. Found 284.0049.

*Ethyl-4-bromo-3-hydroxy-5,6,7,8-tetrahydronaphthalene-2-carboxylate* **(4d):** M.p. 104 °C, yield (96%). $^1$H NMR (300 MHz, $CDCl_3$): δ 11.32 (s, 1H), 7.51 (s, 1H), 4.39 (q, 2H, *J* = 7.35 Hz), 2.78–2.68 (m, 4H), 1.82–1.70 (m, 4H), 1.41 (t, 3H, *J* = 7.36 Hz). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 170.1, 155.0, 145.0, 129.5, 128.5, 113.6, 110.7, 61.7, 31.2, 29.3, 28.4, 22.7, 14.2. MS (*m/z*); 115 (22), 117 (14), 173 (19), 252 (100), 254 (100), 298 ($M^+$, 25). HRMS Calcd for $C_{13}H_{15}BrO_3$ 298.0205. Found 298.0202.

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