Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

# Potassium Fluoride on Alumina: Dry Synthesis of 3-Arylidene-1,3-Dihydro-indol-2-one Under Microwave Irradiation

Didier Villemin [a] & Beno[icaron]t Martin [a]
[a] Ecole Nationale Supérieure d'Ingénieurs de Caen (ISMRA), Universié de Caen, UMR 6507, 6 Boulevard du Marechal Juin F-14050 Caen Cedex, France

Available online: 23 Aug 2006

To cite this article: Didier Villemin & Beno[icaron]t Martin (1998): Potassium Fluoride on Alumina: Dry Synthesis of 3-Arylidene-1,3-Dihydro-indol-2-one Under Microwave Irradiation, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 28:17, 3201-3208

To link to this article: http://dx.doi.org/10.1080/00397919808004422

SYNTHETIC COMMUNICATIONS, 28(17), 3201-3208 (1998)

# POTASSIUM FLUORIDE ON ALUMINA: DRY SYNTHESIS OF 3-ARYLIDENE-1,3-DIHYDRO-INDOL-2-ONE UNDER MICROWAVE IRRADIATION

Didier Villemin* and Benoît Martin

*Ecole Nationale Supérieure d'Ingénieurs de Caen (ISMRA) Université de Caen, UMR 6507, 6 Boulevard du Marechal Juin F-14050 Caen Cedex, France*

**Abstract**: *Aldehydes (2) or ketones (4) were condensed with 1,3-dihydro-indol-2-one (1) in presence of potassium fluoride on alumina without solvent under focused microwave irradiation.*

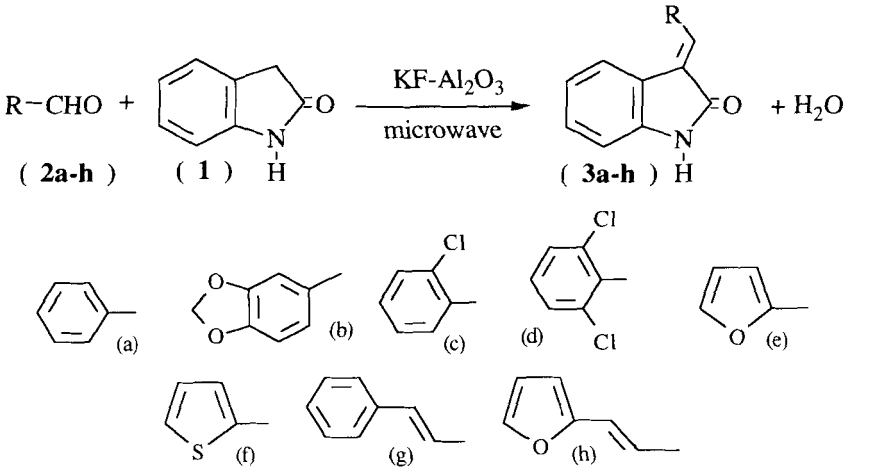


Similar chemical properties have previously been noted [1] between structurally comparable derivatives of 1,2,3,4-tetrahydroisoquinoline-1,3-dione (homophtalimide) and 1,3-dihydro-indol-2-one (oxindole). The condensation of 1,3-dihydro-indol-2-one with carbonyl compounds take place under acidic or basic conditions. The products of condensation are also of interest as intermediates [2] in the synthesis of 2-indolinone alkaloids. The biological properties of arylmethylene-1,3-dihydro-indol-2-ones are poorly studied although that the 2-quinolinemethylene-1,3-dihydro-indol-2-one was reported as tyrosine kinase inhibitor [3a] and 3α-picolylidene-1,3-dihydro-indol-2-one was described as exhibiting strong cholinergic effects [3b].

We have previously described the condensation of 1,2,3,4-tetrahydroisoquinoleine [4] with aromatic aldehydes under microwave irradiation, we described herein the dry condensation of 1,3-dihydro-indol-2-one with

* To whom correspondence should be addressed

**Scheme 1**: Dry condensation of 1,3-dihydro-indol-2-one (**1**) with aldehydes under microwave irradiation.




carbonyl compounds on potassium fluoride on alumina under microwave irradiation according the scheme 1.

### Condensation with aldehydes

The dry condensation of aldehydes (**2a-h**) with 1,3-dihydro-indol-2-one (**1**) under microwave irradiation (2450 MHz) take place without difficulty . The results obtained with different aldehydes and the conditions of the reaction are reported in table 1.

Yields are generally good (81-94%) except for the hindered aldehyde 2,6-dichlorobenzaldehyde (**2d,** 69%). The alkene proton appears in PMR as a singlet between 7.5 and 8.6 ppm for all condensation products. The stereochemistry was attributed by comparison of the PMR spectra of the products obtained and the spectra described in the literature.

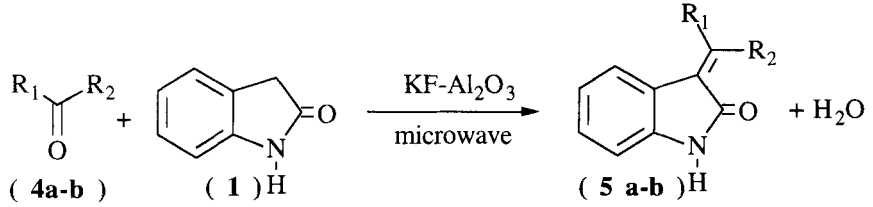
### Condensation with ketones

Although many dry Knoevenagel condensations were described with aldehydes, the condensation with less reactive ketone was not previously reported. The two

**Table 1**: Condensation of 1,3-dihydro-indol-2-one (**1**) with arylcarboxyaldehydes (**2**) under focused microwave irradiation (2450 MHz , 60W).

| Entry | Aldehyde (**2**) | Irradiation (min.) | Yield (%) |
|---|---|---|---|
| a | benzaldehyde | 3 | 94 |
| b | 3,4-(methylenedioxy)benzaldehyde | 3.5 | 92 |
| c | 2-chlorobenzaldehyde | 2.5 | 81 |
| d | 2,6-dichlorobenzaldehyde | 3.5 | 69 |
| e | 2-furannecarboxaldehyde | 5 | 83 |
| f | 2-thiophenecarboxaldehyde | 5 | 85 |
| g | cinnamaldehyde | 6 | 88 |
| h | furylidenecarboxaldehyde | 10 | 81 |

**Scheme 2:** Dry condensation of 1,3-dihydro-indol-2-one (**1**) with ketones under microwave irradiation.




( **4a-b** ) ( **1** ) ( **5 a-b** )

(**a**) ; $R_1$, $R_2$= $(CH_2)_5$; (b) $R_1$=$R_2$= $C_6H_5$

ketones (**5a-b**) can reacted with 1,3-dihydro-indol-2-one (see table 2) after a prolonged microwave irradiation according the scheme 2.

The results obtained here show that the scope of dry Knoevenagel reaction can be extended to reactive ketones. The condensation products of 1,3-dihydro-indol-

**Table 2:** : Condensation of 1,3-dihydro-indol-2-one (**1**) with ketones (**4**) under focused microwave irradiation (2450 MHz ).

| Entry | Ketone (**4**) | Irradiation (W, min.) | Yield (%) |
|---|---|---|---|
| **5a** | cyclohexanone | 40W, 10 min. | 76 |
| **5b** | benzophenone | 100W, 10 min | 35 |



2-one are useful for their biological properties [4,7] or as synthon in organic synthesis[3].

In conclusion the dry condensation of aldehydes and ketones under microwave irradiation is a fast and convenient method for the preparation of 3-arylidene-1,3-dihydroindol-2-ones.

## Experimental

Proton NMR spectra (PMR) in ppm downfield from internal $Me_4Si$ were recorded on a Brucker AC 250 instrument from a solution in DMSO-$d_6$ of the product. Mass spectra were recorded on Nermag R10.10H spectrometer. Melting point (mp) in °C are uncorrected.

*General procedure :*

1,3-Dihydro-indol-2-one (3 mmol, 0.399 g) and the carbonyl compound (3 mmol) were stirred together in 30 ml acetonitrile with 3 g of KF-$Al_2O_3$. After 5 min at room temperature, The solvent was then evaporated in vacuum and the solid was irradiated in an open Pyrex tube 8 mm diameter with focused microwaves in resonance cavity $TE_{01}$ at 2450 MHz, with a universal generator MES 73-800. Extraction was carried out with 40 ml acetonitrile. The product was filtered off and the solvent was evaporated.

### 3-(E)-Benzylidene-1,3-dihydro-indol-2-one (3a)

Obtained from 1,3-dihydro-indol-2-one and benzaldehyde; irradiation 60 W, 3 min; yellow solid; yield 94%; mp 178 (ethanol) (lit. [5]175-176); $C_{15}H_{11}NO$; NMR

$^1H$ ($CDCl_3$) δ: 6.9 (b, 2H, $H_{arom}$), 7.2 (b, 1H, $H_{arom}$), 7.5 (b, 3H, $H_{arom}$), 7.7 (b, 3H, $H_{arom}$), 7.9 (s, 1H, CH=C), 8.6 (b, 1H, NH); MS m/z(%): 222 ($M^{+\cdot}$+1, 29.6), 221 ($M^{+\cdot}$, 100.0), 220 (73.6), 193 (44.0), 175 (34.4), 166 (26.4), 165 (44.0), 144 (31.2), 132 (26.4), 120 (27.2),.

**3-Benzo(1,3) dioxol-5-ylmethylene-1,3-dihydro-indol-2-one (3b)**

Obtained from 1,3-dihydro-indol-2-one and piperonal.; irradiation 60 W, 3 min 30 s; yellow solid; yield 92%; mp 210 (lit .[6] 210-211); $C_{16}H_{11}NO_3$; NMR $^1H$ ($CDCl_3$) δ: 6.05 (s, 2H, $CH_2$), 6.9 to 7.0 (b, 3H, $H_{arom}$), 7.2 to 7.35 (b, 2H, $H_{arom}$), 7.65 to 7.75 (m, 3H, $H_{arom}$ and CH=C); MS m/z(%): 266 ($M^{+\cdot}$+1, 2.9), 265 ($M^{+\cdot}$, 14.2), 264 (6.7), 237 (4.0).

**3-(2-Chloro-benzylidene)-1,3-dihydro-indol-2-one (3c)**

Obtained from 1,3-dihydro-indol-2-one and 2-chlorobenzaldehyde; irradiation 60 W, 2 min 30 s; yellow solid; yield 81%; mp 178 (ethanol) (lit .[7] 178); $C_{15}H_{10}NOCl$; NMR $^1H$ ($CDCl_3$) δ: 6.8 to 7.0 (b, 2H, $H_{arom}$), 7.2 to 7.55 (b, 5H, $H_{arom}$), 7.75 (b, 1H, $H_{arom}$), 7.9 (s, 1H, CH=C), 8.6 (b, 1H, NH); MS m/z (%): 257 (6.6), 256 (2.3), 255 ($M^{+\cdot}$, 10.5), 223 (4.1), 222 (8.2), 221 (18.2), 133 (10.6), 132 (7.3).

**3-(2,6-Dichlorobenzylidene)-1,3-dihydro-indol-2-one (3d)**

Obtained from 1,3-dihydro-indol-2-one and 2,6-dichlorobenzaldehyde; irradiation 60 W, 3 min 30 s; red solid; yield 69%; mp 164; $C_{15}H_9NOCl_2$; NMR $^1H$ ($CDCl_3$) δ: 6.7 (d, 1H, $H_{arom}$, $J_1$=7.5 Hz), 6.8 to 6.9 (b, 2H, $H_{arom}$), 7.2 to 7.7 (b, 3H, $H_{arom}$), 7.95 (d, 1H, $H_{arom}$, $J_2$=8.1 Hz), 8.3 (b, 1H, NH), 8.6 (s, 1H, CH=C); MS m/z (%): 291 ($M^{+\cdot}$+1, 0.3), 289 (0.66), 255 (38.2), 254 (31.4), 253 (100.0).

**3-Furan-2-ylmethylene-1,3-dihydro-indol-2-one (3e)**

Obtained from 1,3-dihydro-indol-2-one and 2-furaldehyde; irradiation 60 W, 5 min; red solid; yield 83%; mp 183 (ethanol) (lit .[8] 178); $C_{13}H_9NO_2$; NMR $^1H$ ($CDCl_3$) δ: 6.65 (b, 1H, $H_{arom}$), 6.9 to 7.0 (b, 2H, $H_{arom}$),7.1 (t, 1H, $H_{arom}$, $J_1$=7.5 Hz), 7.2 to 7.3 (b, 1H, $H_{arom}$),7.5 (s, 1H, CH=C) 7.8(b, 1H, $H_{arom}$) 8.25(b, 1H, NH) 8.5 (d, 1H, $H_{arom}$, $J_2$= Hz); MS m/z (%): 212 ($M^{+\cdot}$+1, 16.1), 211 ($M^{+\cdot}$, 38.7), 189 (16.3), 175 (38.7), 149 (22.6).

**3-Thiophen-2-ylmethylene-1,3-dihydro-indol-2-one (3f)**

Obtained from 1,3-dihydro-indol-2-one and 2-thiophenecarboxaldehyde; irradiation 60 W, 5 min; brown solid; yield 85%; mp 210 (ethanol) (lit .[9] 208-210); $C_{13}H_9NOS$; NMR $^1H$ ($CDCl_3$) δ: 6.9 (b, 1H, H $_{arom}$), 7.1 to 7.3 (b, 4H, H $_{arom}$), 7.6 to 7.7 (b, 2H, H $_{arom}$ and NH), 7.9 (s, 1H, CH=C), 8.9 (d, 1H, H $_{arom}$, $J_2$= 8.1Hz): MS m/z(%): 228 ($M^{+\cdot}$+1, 16.6), 227 ($M^{+\cdot}$, 88.6), 199 (39.0), 198 (27.4), 171 (15.7).

**3-[3-(Fur-2-yl)prop-2-enylidene]-1,3-dihydro-indol-2-one (3h)**

Obtained from 1,3-dihydro-indol-2-one and 3-(2-furyl)acrolein ; irradiation 60 W, 10 min; red solid; yield 81% : mp 193; $C_{15}H_{11}NO_2$; NMR $^1H$ ($CDCl_3$) δ: 6.5(m, 1H, H $_{arom}$), 6.6(m, 1H, H $_{arom}$), 6.85 to 7.55(m, 7H, H $_{arom}$ and H $_{ethyl}$), 7.7(d, 1H, H $_{arom}$, J=7.6 Hz), 7.9(m, 1H, NH); MS m/z (%): 238 ($M^{+\cdot}$+1, 12.8), 237 ($M^{+\cdot}$, 100), 236 (53.8), 220 (28.2), 208 (23.1), 207(17.9), 180 (23.1).

**3-(3-Phenyl-allylidene)-1,3-dihydro-indol-2-one (3g)**

Obtained from 1,3-dihydro-indol-2-one and trans-cinnamaldehyde; irradiation 60 W, 6 min; orange solid; yield 88%; mp 206 (ethanol) (lit.[10] 205-206); $C_{17}H_{13}NO$; NMR $^1H$ ($CDCl_3$) δ: 6.9 (d, 1H, H $_{arom}$, J=7.8 Hz), 7.05 to 7.8 (m, 11H, H $_{arom}$ and H $_{ethyl}$), 8.25 (m, 1H, NH); MS m/z (%): 248 ($M^{+\cdot}$+1, 12.7), 247 ($M^{+\cdot}$, 100), 246 (38.2), 221 (29.1), 220 (18.9), 218 (12.7), 144(12.8).

**3-cyclohexylidene-1,3-dihydro-indol-2-one (5a)**

Obtained from 1,3-dihydro-indol-2-one and cyclohexanone; irradiation 40 W, 10 min; orang solid; yield 76%; mp 191 (lit [11]. 193); $C_{14}H_{15}NO$; NMR $^1H$ ($CDCl_3$) δ: 1.7 to 1.9(m, 10H, $CH_2$), 6.85( d, 1H, H $_{arom}$, J=7.7 Hz), 7.0 (t, 1H, H $_{arom}$, J=7.7 Hz), 7.15 (t, 1H, H $_{arom}$, J=7.7 Hz), 7.65(d, 1H, H $_{arom}$, J=7.7 Hz), 8.0(m, 1H, NH); MS m/z(%): 214 ($M^{+\cdot}$+1, 5.6), 213 ($M^{+\cdot}$, 51.4), 198 (4.9), 146(7.0).

**3-(Diphenylmethylene)-1,3-dihydro-indol-2-one (5b)**

Obtained from 1,3-dihydro-indol-2-one and benzophenone; irradiation 100 W, 10 min; yellow solid; yield 35% ; mp 235° (lit.[12] 240°); $C_{21}H_{15}NO$; NMR $^1H$

($CDCl_3$) δ: 6.6 (d, 1H, $H_{arom}$, J=7,5 Hz), 6.8 (t, 1H, $H_{arom}$, J=7,5 Hz), 7.2 to 7.5 (m, 12H, $H_{arom}$); MS m/z(%): 297 ($M^{+\cdot}$, 100), 296 (40.6), 267 (20.2), 266 (12.5), 265 (12.5), 240 (12.5), 221 (17.2), 220 (57.8), 182 (60.9), 166 (12.5), 105 (50.0).

## References

1. Horning D. E., Lacasse G. and Muchowski J., *Can. J. Chem.*, **1991,** *9*, 246; Elliott, I.W. Jr and Takekoshi Y., *J. Heterocyclic Chem.*, **1976**, *13* 597.

2. Finch N. and Taylor W. I., *J. Am. Chem. Soc.*, **1962**, *84*, 1318 and 3871; Julian P.L., Magnani A., Pikl J. and Karpel W. J., *J. Am. Chem. Soc.*, **1948**, *70*, 174.

3. a) Buzzetti F., Longo A. and Colombo M., *PCT Int. Appl. WO* 91 13,055, *Chem. Abstr.* **1992**, *115*, 279 621q; b) Walker G.N., *J. Org. Chem.*, **1962**, *27*, 2967.

4. Villemin D., Martin B· and Khalid M., *Synth. Commun.*, preceeding paper .

5. Canoira L.and Rodriguez J. G., *J. Heterocycl. Chem.*, **1985**, 22, 1511; Lathourakis G. E.and Litinas K. E., *J. Chem. Soc. Perkin Trans. 1*, **1996**, 491.

6. Abramovitch R. A. and Hey D. H., *J. Chem. Soc.*, **1954**, 1697.

7. Neber P. W. and Roecker E., *Chem.Ber.*; **1923**, *56*, 1710.

8. Kovac J. and Stetinova J., *Chem.Zvesti* , **1976**, *30*, 484.

9. Patent; Squibb; *US Patent* 4002749; **1977**; *Chem.Abstr.*, *86*; 171457.

10. Elliot I.W., Rivers P., *J. Org. Chem.*. **1964**, *29*, 2438.

11. Anthony W.C., *J.Org.Chem.* , **1966**, 31, 77; Walker G.N., Smith R.T. and Weaver B.N., *J. Med. Chem.*, **1965**, 8, 626; Patent Upjohn; *FR* 1445825,

**1966**;*Chem.Abstr.*, **1967**, *66*; 46344; Patent Upjohn, *NL* 6505846; **1966**; *Chem.Abstr. 66*; 104918, **1967**; Patent Upjohn, *US* 3301868; **1967**, *Chem.Abstr.*, **1967**, *67*; 54042;

12. Schönberg A. and Junghaus K., *Chem. Ber.*, **1963**, *96*, 3328.

Accepted February 8, 1998