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Didier Villemin [a] & Beno[icaron]t Martin [a]
[a] Ecole Nationale Supérieure d' Ingénieurs de Caen, I.S.M.R.A., Groupe Catalyse et Modélisation (U.R.A. 480), F-14050, Caen Cedex, France Fax: E-mail:

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DRY CONDENSATION OF CREATININE WITH ALDEHYDES UNDER FOCUSED MICROWAVE IRRADIATION

Didier Villemin* and Benoît Martin

Ecole Nationale Supérieure d' Ingénieurs de Caen,
I.S.M.R.A., Groupe Catalyse et Modélisation (U.R.A. 480)
F-14050 Caen Cedex, France.
fax: 31-45-28-77 / Villemin@ismra.unicaen.fr

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Abstract: *Creatinine was condensed with aromatic aldehydes into Z-arylidene creatinines without solvent under focused microwave irradiation.*

Five ring compounds like tetronic acid[1], pyrazolone[2], coumaranone[3], thiohydanthoin[4], indanone[5], exhibit high carbon acidity due to the pseudoplanar structure and consequently these compounds can be condensed easily with aldehydes in the presence of a weak base without solvent. α-Unsaturated aminoacids are precursors to chiral aminoacids and also have interesting inhibitor enzyme properties. We have already described the synthesis of such α-unsaturated aminoacids with the dry condensation of thiohydantoin[4] with aldehydes and the condensation of diacetylpiperazinedione[6] with aldehydes leading to the synthesis of the antibiotic albonursin.

Creatinine or 2-imino-1-methyl-imidazol-4-one contains a glycine residue and guanidine residue in a five membered ring. In the case of creatinine, the

* To whom correspondence should be addressed

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guanidine part is sufficiently basic (pKb=10.45 at 40°C), so no addition of base was necessary for deprotonation of the glycine residue. Self deprotonation is known[8] to take place and Knoevenagel condensation was observed when creatinine and an aldehyde were heated at 160-170°C.

We report herein the condensation of creatinine with aldehydes under microwave irradiation (scheme 1). Creatinine is a polar molecule which adsorbed efficiently microwaves and as did the water formed in the condensation.

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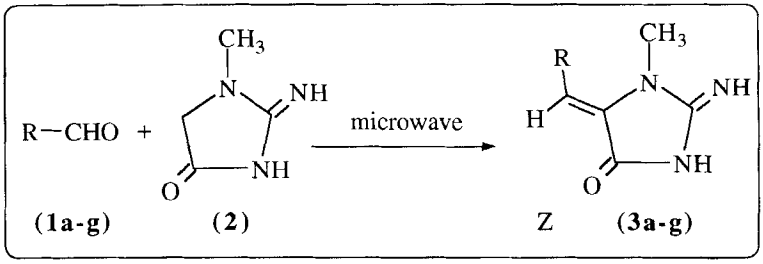
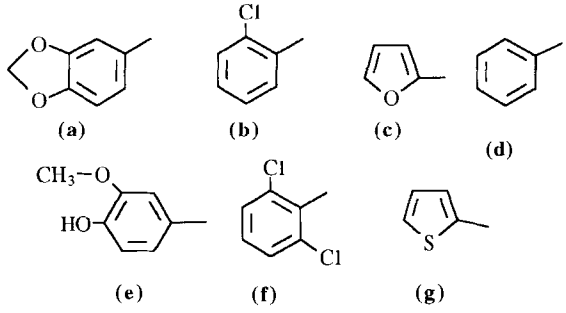
Scheme 1: Condensation of creatinine with aldehydes under microwave irradiation

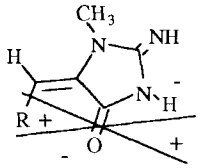




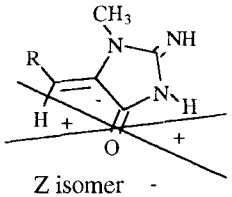
The reaction took place without a catalyst, very rapidly (45s-4 mn) giving a good yield (77-93%). Small traces of secondary product were formed. According to the mass spectra, although pure samples were not obtained, it seemed that a secondary product was formed from two molecules of creatinine and one of

aldehyde. The product described by Cornthwaite and al.[9] as a compound formed by two molecules of the normal condensation product with one molecule of creatinine was not observed.

The reaction was generally stereospecific, only in the case of piperonal (**3a**, 93%Z+7%E) and vanillal (**3e**,98%Z+2%E) derivatives we observed isomers by PNR. The assignation of stereochemistry was based on the shielding effect of the carbonyl group on the olefinic proton. The major or the only isomer was the Z isomer.



E isomer



Z isomer -

δCH:6.40(**3a**) δCH:6.14(**3a**)

δCH:6.45(**3e**) δCH:6.18 (**3e**)

In conclusion, focussed microwave irradiation allows easy synthesis of Z-arylidene creatinine derivatives.

Experimental

Proton NMR spectra (PMR) in ppm downfield from internal Me_4Si were recorded on a Brucker AC 250 instrument from a solution in d^6 -DMSO of the product. Mass spectra were recorded on Nermag R10.10H spectrometer. Melting point (Mp) in °C are uncorrected.

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General procedure:

Creatinine (10^{-3} mol) and solid aldehyde ($1.5.10^{-3}$ mol) were crushed with a mortar and pestle. The mixture was irradiated in an open Pyrex tube 8 mm diameter with focussed microwaves (40 W or 60W) in resonance cavity TE_{01} at 2450 MHz with a universal generator MES 73-800, previously described[7]. The mixture was washed with water and then with ether to remove excess aldehyde. Recrystallisation from alcohol yielded the condensation product.

5-[3,4-(methylenedioxyphenyl)methylene]-2-imino-1-methyl imidazolid-4-one (3a)

Prepared from creatinine and piperonal.

40W, 2 mn 30s; yield=89%; yellow solid; Mp>260°(lit. Mp=274° [9]); $C_{12}H_{11}N_3O_3$; MM=245; NMR ^1H (DMSO-d_6) δ: 3.1(s, 3H, CH_3) 6.0(s, 2H, CH_2) 6.14(s, 1H, CH=C) 6.9(d, 1H, H arom, J=8 Hz) 7.4(d, 1H, H arom, J=8 Hz) 8.35(s, 1H, H arom); MS m/z(%): 246($M^{+\cdot}$+1, 18.6) 245($M^{+\cdot}$, 100.0) 244(27.9) 240(8.1) 239(55.1) 238(14.2) 173(12.1) 135(8.1) 130(12.1) 102(11.7) 77(12.2) 76(24.7).

5-[1-(chlorophenyl)methylene]-2-imino-1-methyl imidazolid-4-one (3b)

Prepared from creatinine and 2-chlorobenzaldehyde.

40W, 2 mn; yield=84%; yellow solid; Mp=248°(lit. Mp=242° [9]); $C_{11}H_{10}N_3OCl$; MM=235; NMR ^1H (DMSO-d_6) δ: 3.2(s, 3H, N-CH_3) 6.2(s, 1H, CH=C) 7.2 to 7.3(br, 1H, H arom) 7.45(br, 1H, H arom) 8.1(br, 1H, H arom); MS m/z(%): 238(23.1) 236(23.0) 215(53.8) 214(46.1) 201(100.0) 197(30.8) 130(23.1) 128(53.9) 125(38.5) 123(69.2) 111(38.5).

5-[furfur-2-yl methylene] 2-imino-1-methyl imidazolid-4-one (3c)

Prepared from creatinine and 2-furaldehyde

40W, 3 mn 30 s; yield=91%; brown solid; Mp>260°(lit. Mp=273° [10]); $C_9H_9N_3O_2$; MM=191; NMR ^1H (DMSO-d_6) δ: 3.2(s, 3H, N-CH_3) 6.15(s, 1H, CH=C) 6.55(br, 1H, H arom) 7.7(br, 1H, H arom) 7.85(br, 1H, H arom); MS m/z(%): 191($M^{+\cdot}$, 19.7) 189(13.6) 188(84.8) 122(13.6) 121(100) 107(15.2) 106(60.6).

5-[phenylmethylene] 2-imino-1-methyl imidazolid-4-one (3d)

Prepared from creatinine and benzaldehyde.

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40W, 2mn; yield=87%; yellow solid; Mp=248 °(lit. Mp=244° [11]); $C_{11}H_{11}N_3O$; MM=201; NMR ^1H (DMSO-d_6) δ: 3.2(s, 3H, CH_3) 6.2(s, 1H, CH=C) 7.2 to 7.4(br, 3H, H arom) 8.1(d, 2H, H arom, J=7 Hz); MS m/z(%): 202($M^{+\cdot}$+1, 2.8) 201($M^{+\cdot}$, 15.8) 200(12.5) 132(8.9) 131(47.4) 116(10.3) 69(25.8).

5-[4-hydroxy-3-methoxy (phenyl)methylene] 2-imino-1-methyl imidazolid-4-one (3e)

Prepared from creatinine and vanillin.

60W, 45 s; yield=91%; orange solid; Mp>260°(lit. Mp=273° [8]); $C_{12}H_{13}N_3O_3$; MM=247; NMR ^1H (DMSO-d_6) δ: 3.2(s, 3H, N-CH_3) 3.8(s, 3H, CH_3O) 6.18(s, 1H, CH=C) 6.75(d, 1 H, H arom, J=8 Hz) 7.35(d, 1H, H arom, J=8 Hz) 8.45(s, 1H, H arom) ; MS m/z(%): 247($M^{+\cdot}$, 44.5) 246(13.6) 241(22.3) 161(45.1) 114(14.8) 113(53.2).

5-[2,6-(dichlorophenyl)methylene] 2-imino-1-methyl imidazolid-4-one (3f)

Prepared from creatinine and 2,5-dichlorobenzaldehyde.

40W, 4 mn; yield=73%; yellow solid; Mp>260°; $C_{11}H_9N_3OCl_2$; MM=270; NMR ^1H (DMSO-d_6) δ: 3.2(s, 3H, N-CH_3) 6.0(s, 1H, CH=C) 7.2 to 7.3(br, 1H, H arom) 7.4 to 7.5(br, 2H, H arom); MS m/z(%): 236(20.7) 235(18.4) 234(62.9) 233(14.1) 232(12.9) 184(10.7) 182(16.6) 113(14.6).

5-[thien-2-yl methylene] 2-imino-1-methyl imidazolid-4-one (3g)

Prepared from creatinine and 2-thiophenecarboxaldehyde.

40W, 3mn 15 s; yield=93%; brown solid; Mp>260°(lit. Mp= 279° [12]); $C_9H_9N_3OS$; MM=207; NMR ^1H (DMSO-d_6) δ: 3.2(s, 3H, N-CH_3) 6.55(s, 1H, CH=C) 7.05(dd, 1H, H arom, J_1=3Hz,, J_2=5 Hz) 7.5(d, 1H, H arom, J_2=5 Hz) 7.65(d, 1H, H arom, J_1=3 Hz); MS m/z(%): 208($M^{+\cdot}$+1, 6.2) 207($M^{+\cdot}$, 100.0) 206(19.1) 203(35.8) 137(19.9) 122(53.4) 113(9.1) 112(17.9).

All the NH protons have a chemical shift between 7.5 and 8.0 p.p.m.

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