Behaviour of 3(3-indolylmethylene)-5-aryl-2(3*H*)-furanones as alkylating agents: intra- versus inter-molecular alkylation

Wael S.I. Abou-Elmagd*

Chemistry Department, Faculty of Science, Ain Shams University, Abassia, Cairo, Egypt

5-Aryl-3-(3-indolylmethylene)-2(3*H*)-furanones (**6a–c**) were prepared as a mixture of (*E*) and (*Z*) stereoisomers by condensing indole-3-carboxaldehyde with 3-aroylpropanoic acids using thionyl chloride in *N,N*-dimethylformamide as cyclodehydrating agent. The reaction of the furanones **6a** and **6b** with anhydrous aluminium chloride in benzene, toluene or anisole led to the formation of 4,4-diaryl-1-(3-indolyl)buta-1,3-diene-2-carboxylic acids (**7**) as mixtures of geometrical (*E*, *E*- and *E*, *Z*-) stereoisomers via an intermolecular alkylation mode. The furanone **6c** under the same reaction conditions gave 1-(4-methoxyphenyl)carbazole-3-carboxylic acid (**8**) via intramolecular alkylation. This represents a novel method for the synthesis of carbazole derivatives.

Keywords: 2(3H)-furanones, indoles, 1,3-butadienes, carbazoles, electrophilic alkenylation

The behaviour of 2(3*H*)-furanones (**1**) as alkylating agents had been of interest to our research group. It has been found that aluminium chloride in the presence of benzene, toluene or anisole effected alkyl–oxygen cleavage of the furanone ring to give a resonance-stabilised carbocation (**2**). This carbocation is able to follow two distinct courses: it may either attack the ortho-position (*) intramolecularly to give **3** and **4**, or attack the solvent to give the corresponding butadienecarboxylic acids (**5**) via an intermolecular alkylation reaction.

Thus, when X was a fluorenylidene group (**1a**), benzene served simply as a solvent, and intramolecular alkylation led to the formation of fluoranthenecarboxylic acids (**4**).[1] But in toluene or anisole, the products of intermolecular alkylation (**5a**) were obtained.[2] However, when X was 2-furylmethylene[3] (**1b**) or 2-thienylmethylene[4] (**1c**), the products of intramolecular alkylation, the benzofuran and benzothiophene carboxylic acids (**3**, Z = O and S, respectively), were the only isolable products, whatever the nucleophilicity of the solvent. More recently, the reaction of 3-(1,3-diphenylpyrazol-4-ylmethylene)-5-aryl-2(3*H*)-furanones (**1d**) with aluminium chloride in the presence of benzene, toluene or anisole was studied, and exclusively the products of intermolecular alkylation (**5d**) were isolated; no cyclisation to the pyrazole ring was found.[5]

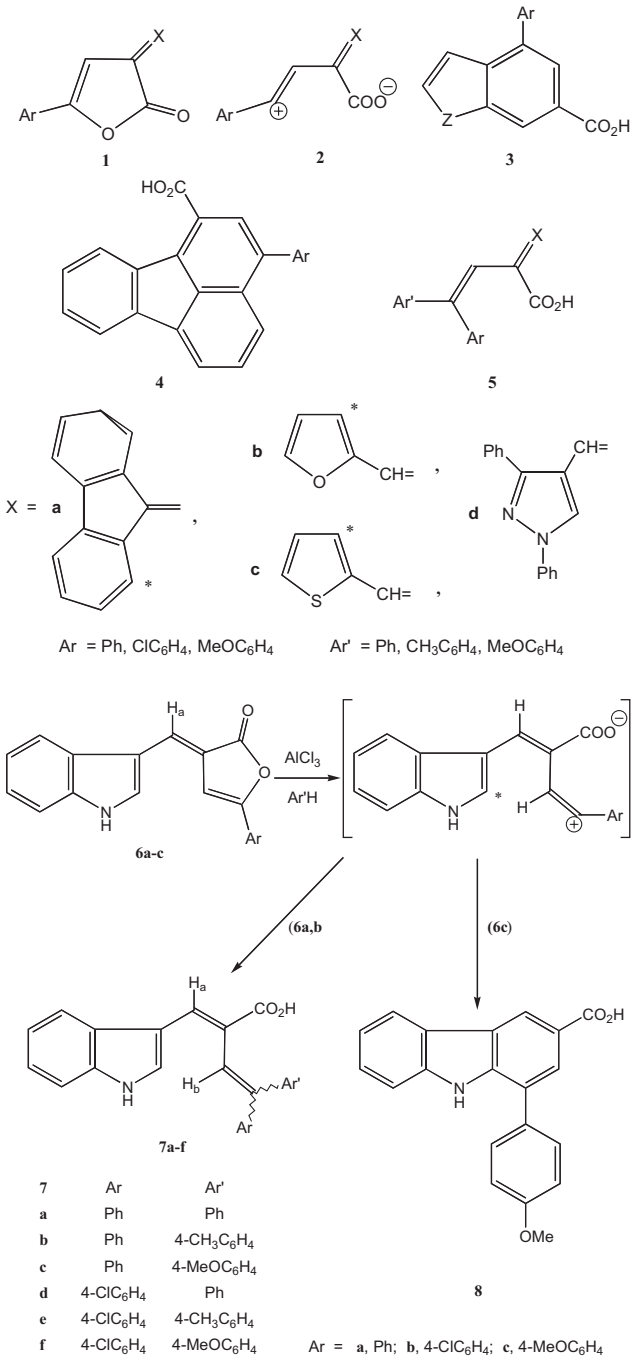
In brief, the behaviour of 2(3*H*)-furanones as alkylating agents seems to depend on two factors: (i) the nature of the aryl group at position **3**,[6] and (ii) the nucleophilicity of the solvent.

It was of interest to the author to investigate the behaviour of newly synthesised 2(3*H*)-furanones, namely the 3-(3-indolylmethylene)-5-aryl-2(3*H*)-furanones (**6a–c**), in the above reaction.

Results and discussion

The furanones **6a–c** were prepared by condensing indole-3-carboxaldehyde with 3-aroylpropionic acids using thionyl chloride in *N,N*-dimethylformamide as a cyclodehydrating agent.[7] The structures of **6** were inferred from their analytical and spectral data (*cf.* Experimental section). The ^{1}H NMR spectra of compounds **6** showed two singlets for the olefinic proton H_a, as well as two singlets for OCH_3 protons in case of **6c**. This showed that compounds **6a–c** were formed as a mixture of two geometrical (*E*- and *Z*-) isomers in which the *E*-isomers predominate.

The furanones **6a**,**b** reacted with $AlCl_3$ in excess of benzene, toluene or anisole to give the butadienecarboxylic acids **7** *via* an intermolecular alkylation mode. (Scheme 1) The furanones are firstly converted by alkyl–oxygen ring cleavage into



7	Ar	Ar'
a	Ph	Ph
b	Ph	4-$CH_3C_6H_4$
c	Ph	4-$MeOC_6H_4$
d	4-ClC_6H_4	Ph
e	4-ClC_6H_4	4-$CH_3C_6H_4$
f	4-ClC_6H_4	4-$MeOC_6H_4$

Scheme 1

* Correspondent. E-mail: waelmagd97@yahoo.com

resonance-stabilised carbocations, which by electrophilic attack on the solvent afforded **7**.

In contrast, when **6c** was allowed to react under the same conditions, the reaction followed another route, to give the carbazole derivative **8**. Evidently this product is formed on the basis of electrophilic attack of the carbocationic centre onto the 2-position of the indole moiety in an intramolecular alkenylation reaction in which the benzene, toluene or anisole served only as solvents without any incorporation into the product of the reaction. When the reaction of the furanone **6c** with aluminium chloride was carried out in tetrachloroethane and nitrobenzene as solvents the same carbazole derivative (**8**) was formed. It is noteworthy that no intramolecular cyclisation products were formed when the furanones **6a**,**b** were treated with aluminium chloride in these solvents.

The structures of the acids **7** followed from the analytical and mass spectroscopic data which indicated the incorporation of a phenyl group in **7a**,**d**, a tolyl group in **7b**,**e**, and the anisyl group in **7c**,**f**, and no solvent incorporation in the product from **6c**. The IR spectra of these acids showed broad bands in the region 2500–3500 cm^{-1} characteristic of the hydrogen bonded –OH moiety of the carboxyl group, and a band at *ca* 1690 cm^{-1} for the carbonyl of the same group.

The ^1H NMR spectra of compounds **7b**–**f** showed two singlets for the olefinic protons, as well as, two singlets for OCH_3 protons in case of **7c**,**f** and two singlets for CH_3 protons in case of **7b**,**e**. This showed that compounds **7b**–**f** exist as a mixture of two geometrical (*E*, *E*) and (*E*, *Z*) stereoisomers in which the latter predominate. The lower proportion, as well as the deshielding of the olefinic proton, in the case of the (*E*, *E*) isomers as compared with their (*E*, *Z*) counterparts can be rationalised in terms of steric considerations and the ring current of the more activated aryl groups, respectively. The ^1H NMR spectra of compound **8** showed the absence of the olefinic proton and the appearance of the carboxylic proton at δ = 12.56 ppm.

This difference in behaviour in the case of **6c**, *i.e.* the preference for the intramolecular pathway, may be explained on the basis of the stabilisation of the carbocation **2** (X = 3-indolylmethylene) afforded by the 4-methoxyphenyl group. Such stability will decrease the reactivity of this carbocation and hence increase its selectivity towards the formation of the more stable carbazole derivative.

In summary, the results obtained here reveal the following:
(1) It is the first time that the nature of the substituent at position **5** of the furanone has affected the mode of reaction with aluminium chloride.
(2) It is evident that the reaction of **6c** with aluminum chloride represents a novel and convenient method for the synthesis of carbazole derivatives, since the furanones are easily prepared from 3-aroylpropanoic acids.

Experimental

Melting points were measured on an electrothermal melting point apparatus. Elemental analyses were carried out at the Microanalytical Unit of Cairo University. IR spectra were measured on a Unicam SP-1200 spectrophotometer using KBr wafer technique. ^1H NMR spectra were measured in DMSO–d_6 on a Varian Plus instrument (300 MHz). Mass spectra were recorded on a Shimadzu GC-MS QP1000 EX instrument operating at 70eV in EI mode.

Preparation of 5-aryl-3-(3-indolylmethylene)-2(3H)-furanones (**6a–c**)
(i) (Chlorosulfinyloxy)-*N*,*N*-dimethylmethaniminium chloride (the cyclodehydrating agent): Into a 25 ml dropping funnel containing benzene (5 ml), *N*,*N*-dimethylformamide (1 ml, 10.2 mmole) was added, followed by thionyl chloride (0.8 ml, 11 mmole). After 5 minutes the two phases were separated, and the reagent (lower layer) was used in the next step.

(ii) To a stirred solution of 3-aroylpropanoic acid (10 mmole) in dichloromethane (25 ml) at 0°C, the cyclodehydrating agent (10 mmole) prepared in step (i) was added. Stirring was continued for 15 min. Indole-3-carboxaldehyde (1.45 g, 10 mmole) was added followed by triethylamine (30 mmole) in dichloromethane (15 ml). The resulting mixture was stirred at room temperature for 5 hr. The organic layer was washed with water (2 × 50 ml) and dried over anhydrous sodium sulfate. Removal of the solvent left a residue which formed golden yellow crystals when recrystallised from ethanol.

5-Phenyl compound (**6a**): 85% yield, m.p. 190–192°C. IR: ν_{max} 3414 (NH), 1756 (C=O), 1590 (C=C) cm^{-1}. ^1H NMR (DMSO-d_6): (*E*-form, 75%) δ 7.42–7.96 (m, NH + 11 Ar H), 8.42 (s, 1H, H_a); (*Z*-form, 25%) δ 8.37 (s, 1H, H_a) MS: *m/z* (%) 287 (M^+, 67), 259 (45), 241 (13), 230 (45), 154 (100), 145 (29), 105 (31), 95 (46), 77 (24), 51 (39). Anal. Calcd for $C_{19}H_{13}NO_2$: C, 79.44; H, 4.53; N, 4.88. Found: C, 79.72; H, 4.40; N, 4.60%.

5-(4-Chlorophenyl) compound (**6b**): 80% yield, m.p. 204–206°C. IR: ν_{max} 3422 (NH), 1760 (C=O), 1589 (C=C) cm^{-1}. ^1H NMR (DMSO-d_6): (*E*-form, 75%) δ 7.23–7.94 (m, NH + 10Ar H), 8.39 (s, 1H, H_a); (*Z*-form, 25%) δ 8.34 (s, 1H, H_a) MS: *m/z* (%) 323 (13), 321 (M^+, 47), 293 (26), 154 (100), 145 (36), 144 (48), 139 (26), 85 (27), 49 (21). Anal. Calcd for $C_{19}H_{12}ClNO_2$: C, 71.03; H, 3.74; N, 4.36. Found: C, 71.15; H, 3.65; N, 4.27%.

5-(4-Methoxyphenyl) compound (**6c**): 79% yield, m.p. 198–200°C. IR: ν_{max} 3402 (NH), 1758 (C=O), 1598 (C=C) cm^{-1}. ^1H NMR (DMSO-d_6): (*E*-form, 60%) δ 3.90 (s, 3H, OCH_3), 7.39-8.50 (m, NH + 10ArH), 8.91 (s, 1H, H_a); (*Z*-form, 40%) δ 8.89 (s, 1H, H_a). MS: *m/z* (%): 317 (M^+, 2),287 (22), 230 (22), 188 (27), 146 (36), 145 (100), 144 (59), 143 (51), 89 (23), 43 (31). Anal. Calcd for $C_{20}H_{15}NO_3$: C, 75.71; H, 4.73; N, 4.42%. Found: C, 75.49; H, 4.65; N, 4.35%.

*4,4-Diaryl-1-(3-indolyl)buta-1,3-diene-2-carboxylic acids (7**a–f**) and 1-(4-methoxyphenyl)carbazole-3-carboxylic acid* (**8**)
To a stirred mixture of anhydrous $AlCl_3$ (0.03 mole) in dry benzene, toluene, or anisole (100 ml), a solution of the furanone **6** in benzene, toluene or anisole was added dropwise at 10–20°C. After complete addition the reaction mixture was stirred at room temperature for an additional 15 h. The complex formed was decomposed with 15% aqueous HCl and then steam-distilled to remove the excess of organic solvent. The solid remaining was filtered off, dissolved in aqueous sodium carbonate (25 ml, 20%), cooled well, and reprecipitated by dropwise addition of conc. HCl. The solid product obtained was recrystallised from the specified solvent to give 4,4-diaryl-1-(3-indolyl)buta-1,3-diene-2-carboxylic acids (**7a–f**) in the case of **6a,b** and 1-(4-methoxyphenyl)carbazole-3-carboxylic acid (**8**) in case of **6c**.

Diene acid **7a** (Ar = Ar' = C_6H_5): Yellow crystals (45% yield), m.p. 233–235°C (benzene/ethanol). IR: ν_{max} 2926–3500 (OH), 3334 (NH), 1701(C=O), 1596 (C=C) cm^{-1}. ^1H NMR (DMSO-d_6): δ 6.51 (s,1H, H_a), 6.71–7.52 (m, NH + 15ArH), 8.01 (s, 1H, H_b), 12.60 (br.s, 1H, exchangeable). MS: *m/z* (%) 365 (M^+, 27), 322 (47), 273 (26), 259 (34), 239 (20), 206 (46), 160 (60), 145 (20), 130(100),115 (48), 91(30). Anal. Calcd for $C_{25}H_{19}NO_2$: C, 82.19; H, 5.21; N, 3.84. Found: C, 81.80; H, 5.09; N, 3.72%.

Diene acid **7b** (Ar = C_6H_5, Ar' = 4-$CH_3C_6H_4$): Yellow crystals (40% yield), m.p. 320–323°C (benzene/ethanol). IR: ν_{max}: 2800–3490 (OH), 3362 (NH), 1689 (C=O), 1612 (C=C) cm^{-1}. ^1H NMR (DMSO-d_6): (*E*,*Z*-form, 65%) δ 2.10 (s, 3H, CH_3), 6.34 (s, 1H, H_a), 7.04–7.49 (m, NH + 14ArH), 8.45 (s, 1H, H_b), 12.09 (br.s, 1H, exchangeable); (*E*,*E*-form, 35%) δ 2.13 (s, 3H, CH_3), 8.49 (s, 1H, H_b). MS: *m/z* (%): 379 (M^+, 17), 174 (24), 161 (15), 145 (15), 143 (30),130 (100), 118 (38), 91 (34). Anal. Calcd for $C_{26}H_{21}NO_2$: C, 82.32; H, 5.54; N, 3.69. Found: C, 82.15; H, 5.42; N, 3.50%.

Diene acid **7c** (Ar = C_6H_5, Ar' = 4-$MeOC_6H_4$): Yellowish-white crystals (25% yield) m.p. 340–341°C (ethanol). IR: ν_{max}: 2900–3500 (OH), 3421 (NH), 1706 (C=O), 1582 (C=C) cm^{-1}. ^1H NMR (DMSO-d_6): (*E*,*Z*-form, 60%): δ 3.45 (s, 3H, OCH_3), 6.30 (s, 1H, H_a), 6.51–7.29 (m, NH + 14 ArH), 8.38 (s, 1H, H_b), 12.50 (br.s, 1H, exchangeable); (*E*,*E*-form, 40%): δ 3.41 (s, 3H, OCH_3), 8.39 (s, 1H, H_b). MS: *m/z* (%) 395 (M^+, 36), 378 (11), 252 (37), 184 (25), 174 (29), 141 (27), 130(100), 117 (64), 115 (55), 91 (69), 55 (28). Anal. Calcd for $C_{26}H_{21}NO_3$: C, 78.99; H, 5.32; N, 3.54. Found: C, 78.68; H, 5.60; N, 3.48%.

Diene acid **7d** (Ar = 4-ClC_6H_4, Ar' = C_6H_5: Yellow crystals (35% yield), m.p. 265–266°C (ethanol). IR: ν_{max} 2920–3450 (OH), 3360 (NH), 1705 (C=O), 1587 (C=C) cm^{-1}. ^1H NMR (DMSO-d_6): (*E*, *Z*-form, 70%) δ 6.50 (s,1H, H_a), 6.90–7.99 (m, NH + 14ArH), 8.52 (s, 1H, H_b), 12.22 (br.s, 1H, exchangeable); (*E*,*E*-form, 30%) δ 8.50

(s, 1H, H_b). MS: *m/z* (%): 401 (6.4), 399 (M^+,18), 200 (12), 185 (11), 174 (30), 143 (31), 132 (25), 130 (75), 118 (100), 117 (65), 91 (73), 43 (24). Anal. Calcd for $C_{25}H_{18}ClNO_2$: C, 75.19; H, 4.51; N, 3.51. Found C, 75.37; H, 4.29; N, 3.60%.

Diene acid **7e** (Ar = 4-ClC_6H_4, Ar = 4-$CH_3C_6H_4$): Yellow crystals (30% yield), m.p. 350–353°C (benzene). IR: ν_{max} 2923–3490 (OH), 3360 (NH), 1704 (C=O), 1583 (C=C) cm^{-1}. ^1H NMR (DMSO-d_6): (*E*,*Z*-form, 55%): δ 2.10 (s, 3H, CH_3), 6.62 (s, 1H, H_a), 6.87–7.14 (m, NH + 13ArH), 8.59 (s, 1H, H_b), 11.92 (br.s, 1H, exchangeable); (*E*,*E*-form, 45%) δ 2.09 (s, 3H, CH_3), 8.56 (s, 1H, H_b). MS: *m/z* (%): 415 (17), 413 (M^+, 45), 167 (13), 165 (32), 152 (19), 143 (26), 130 (64), 118 (100), 115 (55), 91 (92), 62 (33). Anal. Calcd for $C_{26}H_{20}ClNO_2$: C, 75.54; H, 4.84; N, 3.39. Found C, 74.95; H, 4.72; N, 3.26%.

Diene acid **7f** (Ar = 4-ClC_6H_4, Ar = 4-$CH_3OC_6H_4$): Yellow crystals (28% yield), m.p. > 360°C (ethanol). IR: ν_{max} 2850–3500 (OH), 3360 (NH), 1699 (C=O), 1590 (C=C) cm^{-1}. ^1H NMR (DMSO-d_6): (*E*,*Z*-form, 60%): δ 3.35 (s, 3H, OCH_3), 6.53 (s, 1H, H_a), 6.92–7.80 (m, NH + 13 ArH), 8.20 (s, 1, H_b), 10.85 (br.s, 1H, exchangeable); (*E*,*E*-form, 40%) δ 3.32 (s, 3H, OCH_3), 8.19 (s, 1H, H_b). MS: *m/z* (%) 431 (5), 429 (M^+,16), 401 (11), 313 (12), 306 (9), 304 (21), 230 (16), 228 (43), 221 (46),217 (45), 214 (70), 181 (100), 165 (72), 152 (75), 145 (44). Anal. Calcd for $C_{26}H_{20}ClNO_3$: C, 72.73; H, 4.66; N, 3.26. Found: C, 71.90; H, 4.35; N, 3.09%.

1-(4-Methoxyphenyl)carbazole-3-carboxylic acid (**8**): Yellow crystals (40% yield), m.p. 280–283°C (ethanol). IR: ν_{max} 2900–3450 (OH), 3420 (NH), 1702 (C=O), 1600 (C=C) cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.66 (s, 3H, OCH_3), 6.80–7.14 (m, 11, NH + 10 ArH), 12.56 (br.s, 1H, exchangeable). MS: *m/z* (%) 317 (M^+, 24), 305 (31), 292 (18), 291 (42), 174 (25), 143 (26), 130 (100), 118(59), 77(39). Anal. Calcd for $C_{20}H_{15}NO_3$: C, 75.71; H, 4.73; N, 4.42. Found: C, 74.98; H, 4.92; N, 4.30%.

Reaction of the furanones **6** *with anhydrous $AlCl_3$ in tetrachloroethane or nitrobenzene*

The reaction was carried out as described in the previous experiment, but using tetrachloroethane or nitrobenzene instead of benzene, toluene or anisole. The product in each case was shown by direct comparison (m.p., mixed m.p. and TLC) to be the unreacted furanone in the case of **6a–b** and the carbazole **8** in the case of **6c**.

Received 25 January 2007; accepted 2 June 2007
Paper 07/4431 doi: 10.3184/030823407X217652

References

1 A.I. Hashem and Z.M. Ismail, *Indian J. Chem.*, 1974, **12**, 902.
2 A.I. Hashem and E.F. Eid, *Indian J. Chem*., 1978, **16**, 502.
3 A.I. Hashem, *J. Prakt. Chem*., 1977, **319**, 689.
4 A.I. Hashem, S.M. El-Kousy, A.M. El-Torgoman and A.M. El-Bassiouny, *Int. J. Chem*., 1991, **2**, 87.
5 A.I. Hashem, K.A. Kandeel, A.S.A. Youssef and W.S.I. Abou-Elmagd, *J. Chem. Res.*, 2006, 315.
6 R. Filler and H.A. Leiplod, *J. Org. Chem*., 1962, **27**, 4440.
7 R.H. Khan and R.C. Rastogi, *J. Chem. Res. (S)*, 1991, 260.