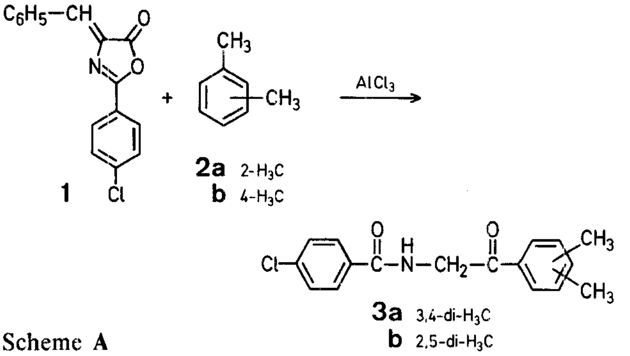
Synthesis of Some 2-Substituted 5-Oxo-4,5-dihydro-1,3-oxazoles and their Ring Cleavage Reactions with Aromatic Hydrocarbons

M. A. El-Hashash, A. A. Afify, A. M. Kaddah, S. S. El-Kady

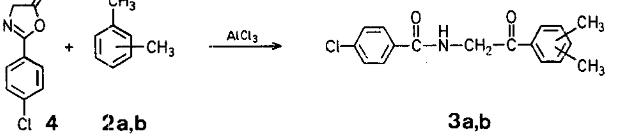
Chemistry Department, Faculty of Science, Ain Shams University, Abbassia, Cairo, A. R. Egypt

We report here on the ring cleavage reactions of 4-benzylidene-2-(4-chlorophenyl)-5-oxo-4,5-dihydro-1,3-oxazole (**1**) with activated aromatic hydrocarbons **2** under Friedel-Crafts conditions to give open-chain products. The oxazole **1** was prepared from 4-chlorobenzoylglycine and benzaldehyde in the presence of acetic anhydride and sodium acetate[1]. Treatment of **1** with *o*- or *p*-xylene (**2a** or **b**) in the presence of aluminium chloride (3 equiv) at 100 °C proceeds by hetero-ring opening and subsequent dearylation to give the *N*-aroylmethyl-4-chlorobenzamides **3a, b** (Scheme **A**).



Scheme **A**

The structures of compounds **3** were further confirmed by an independent synthesis from 2-(4-chlorophenyl)-5-oxo-4,5-dihydro-1,3-oxazole (**4**) and **2a** or **2b** in the presence of aluminium chloride (3 equiv) (Scheme **B**).



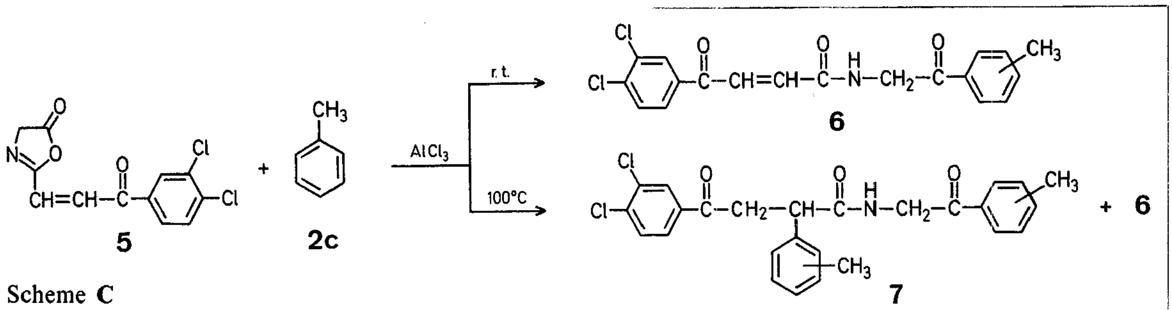
Scheme **B**

It has been previously reported that 2-substituted 4*H*-3,1-benzoxazin-4-ones undergo ring opening reactions with aromatic hydrocarbons[2,3]. Recently, the alkylation of aromatic hydrocarbons with *β*-(3,4-dichlorobenzoyl)-acrylic acid has been studied[4,5].

0039-7881/81/1032-0798 $ 03.00

We have now prepared 2-[3-(3,4-dichlorophenyl)-3-oxopropenyl]-5-oxo-4,5-dihydro-1,3-oxazole (**5**) from β-(3,4-dichlorophenyl)-acryloyl chloride and glycine in the presence of cold potassium hydroxide solution and subsequent treatment with acetic anhydride. This compound contains two possible sites for Friedel-Crafts reactions.

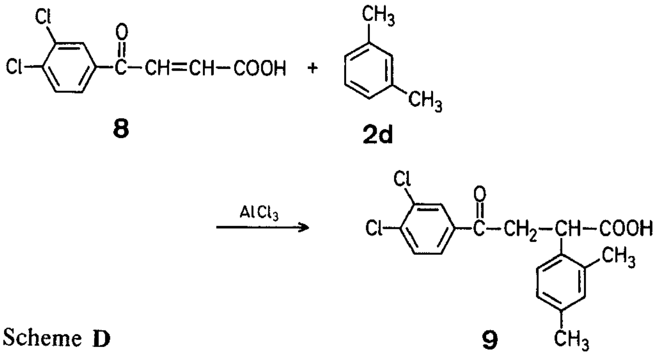
Reaction of **5** with toluene (**2c**) in the presence of aluminium chloride (3 equiv) at room temperature gives *N*-(4-methylbenzoylmethyl)-β-(3,4-dichlorobenzoyl)-acrylamide (**6c**) as the sole product. However, when the reaction is carried out at 100 °C using 6 equivalents of aluminium chloride, *N*-(4-methylbenzoylmethyl)-2-(4-methylphenyl)-3-(3,4-dichlorophenyl)-propanamide (**7c**) is the main product in addition to small amounts of **6c** (Scheme **C**).



Scheme **C**

The oxazolone **5** reacts similarly with *o*-xylene (**2a**) at room temperature in the presence of aluminium chloride (3 equiv) to give the corresponding 3,4-dimethylbenzoylmethyl (**6a**) and 2,3-dimethylbenzoylmethyl (**6e**) alkenamide derivatives. However, reaction of **5** with **2a** at 100 °C in the presence of aluminium chloride (6 equiv) gave the 3,4-dimethylbenzoylmethyl alkanamide derivative **7a** together with small amounts of **6a**. In the case of **7a**, further structural confirmation was obtained by treating **6a** with **2a** in the presence of aluminium chloride (3 equiv) at room temperature or 100 °C while bubbling hydrogen chloride gas through the mixture to give **7a**; thus also indicating that **6a** is an intermediate in the formation of **7a**.

Reaction of **5** with *m*-xylene (**2d**) in the presence of aluminium chloride (3 equiv) both at room temperature and at 100 °C gave the 2,4-dimethylbenzoylmethyl alkanamide derivative **7d**. Further confirmation of the structure of **7d** was obtained by its hydrolysis with boiling hydrochloric acid/acetic acid[6] to give 2-(2,4-dimethylphenyl)-4-(3,4-dichlorophenyl)-4-oxobutanoic acid (**9**), which can be prepared unambiguously from *m*-xylene (**2d**) and 4-(3,4-dichlorophenyl)-4-oxo-2-butenoic acid[4] (**8**) in the presence of aluminium chloride (4 equiv) (Scheme **D**).



Scheme **D**

Reaction of **5** with *p*-xylene (**2b**) under the same conditions at room temperature affords the 2,5-dimethylbenzoylmethyl alkenamide derivative **6b** together with small amounts of the corresponding alkanamide **7b**. On reaction at 100 °C, **7b** is the sole product.

The structures of all compounds prepared were confirmed by microanalytical, I.R. spectral, and ^{1}H-N.M.R. spectral data.

Melting points are not corrected; I.R. spectra were recorded as KBr discs using a Pye-Unicam spectrophotometer; microanalyses were performed by the El-Nasr Company. Friedel-Crafts reactions were carried out in three-necked flasks fitted with a reflux condenser topped with a drying tube, a mechanical stirrer, and a solid addition funnel for aluminium chloride and the aromatic hydrocarbon.

4-Benzylidene-2-(4-chlorophenyl)-5-oxo-4,5-dihydro-1,3-oxazole (1):
A mixture of benzaldehyde (10 g, 0.1 mol), 4-chlorobenzoylglycine (21.3 g, 0.1 mol), acetic anhydride (10 g, 0.1 mol), and fused sodium acetate (0.8 g, 0.01 mol) is heated on a steam bath for 1 h and then cooled. The solid product is filtered and recrystallised from benzene to give **1**; yield: 20.1 g (71%); m.p. 177 °C (Ref.[7], m.p. 178 °C).

***N*-[2-(3,4-Dimethylphenyl)-2-oxoethyl]-4-chlorobenzamide (3a):**
A stirred solution of compound **1** (2.83 g, 0.01 mol) in *o*-xylene (**2a**; 50 ml) is treated portionwise with anhydrous aluminium chloride (4.0 g, 0.03 mol). Stirring is continued at room temperature for 10 h. The mixture is then added to concentrated hydrochloric acid (20 ml)/ice (100 g). The organic layer is separated, washed with water (2 x 100 ml), and excess **2a** is removed by steam distillation. The solid which separates is crystallised from benzene/petroleum ether (b.p. 80-100 °C) to give **3a**; yield: 1.9 g (62%); m.p. 145 °C.

$C_{17}H_{16}ClNO_2$	calc.	C 67.66	H 5.30	N 4.64
(301.8)	found	68.08	5.30	4.42

^{1}H-N.M.R. (CDCl$_3$): δ = 2.10 (s, 3H); 2.30 (s, 3H); 2.90 (s, 2H); 7.0-7.9 (m, 7H); 8.1 ppm (s, 1H).

***N*-[2-(2,5-Dimethylphenyl)-2-oxoethyl]-4-chlorobenzamide (3b):**
Prepared analogously using *p*-xylene (50 ml) and crystallised from petroleum ether (b.p. 80-100 °C); yield: 2.0 g (67%); m.p. 152 °C.

$C_{17}H_{16}ClNO_2$	calc.	C 67.66	H 5.30	N 4.64
(301.8)	found	68.22	5.58	4.48

The I.R. spectra of **3a** and **3b** are similar:
I.R. (KBr): ν = 3200 (NH); 1690-1680 (C=O); 1650-1640 cm^{-1} (C=O).

2-(4-Chlorophenyl)-5-oxo-4,5-dihydro-1,3-oxazole (4):
A mixture of *p*-chlorobenzoylglycine (6.4 g, 0.03 mol) and acetic anhydride (30 ml) is heated under reflux for 1 h. The mixture is allowed to cool and the flask scratched to induce crystallisation. The solid is filtered, washed with petroleum ether (b.p. 40-60 °C), and dried; yield: 5 g (86%); m.p. 127 °C (Ref.[1], m.p. 125 °C).

Benzamides 3a, b from Oxazole 4:
Aluminium chloride (4.0 g, 0.03 mol) is added to a vigorously stirred solution of **4** (2 g, 0.01 mol) in *o*-xylene or *p*-xylene (150 ml) as described above for **3a**. The solid product obtained is crystallised from the appropriate solvent and identified by m.p. and m.m.p. measurement.

2-[3-(3,4-Dichlorophenyl)-3-oxopropenyl]-5-oxo-4,5-dihydro-1,3-oxazole (5):
3,4-Dichlorobenzoylacryloylglycine: 4-(3,4-Dichlorophenyl)-4-oxo-2-butenoic acid (**8**; 4.9 g, 0.02 mol) in dry benzene is treated with pyrid-

Table. Reactions of 2-[3-(3,4-Dichlorophenyl)-3-oxopropenyl]-5-oxo-4,5-dihydro-1,3-oxazole **5** with Aromatic Hydrocarbons **2** in the Presence of Aluminium Chloride

Aromatic hydrocarbon **2**	Reaction Conditions (temperature/ equiv of $AlCl_3$)	Product No.	Position of CH_3	Yield [%]	m.p. [°C] (solvent)	Molecular formula[a]	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. δ [ppm]
o-xylene **(2a)**	r.t./3	**6a**	3,4-di-CH_3	66	142° (C_6H_6)	$C_{20}H_{17}Cl_2NO_3$ (390.3)	3250-3100, 1690-1680,	—
		+						
		6e	2,3-di-CH_3	13	105° (80-100° PE)	$C_{20}H_{17}Cl_2NO_3$ (390.3)	1670-1665, 1650	
o-xylene **(2a)**	100°C/6	**7a**	3,4-di-CH_3	15	220° (AcOH)	$C_{28}H_{27}Cl_2NO_3$ (496.4)	3250-3100, 1690-1680, 1670-1665, 1650, 770, 690	—
		+						
		6a	3,4-di-CH_3	8	see above	—	—	—
p-xylene **(2b)**	r.t./3	**6b**	2,5-di-CH_3	58	150° (100-120° PE)	$C_{20}H_{17}Cl_2NO_3$ (390.3)	—	—
		+						
		7b	2,5-di-CH_3	23	see below	—	—	—
p-xylene **(2b)**	100°C/6	**7b**	2,5-di-CH_3	42	165° (C_6H_6)	$C_{28}H_{27}Cl_2NO_3$ (496.4)	3100, 1700, 1690, 1650	—
toluene **(2c)**	r.t./3	**6c**	4-H_3C	65	194° (C_6H_6)	$C_{19}H_{15}Cl_2NO_3$ (376.2)	~3200, 1695, 1670, 1640	—
toluene **(2c)**	100°C/6	**7c**	4-H_3C	66	215° (toluene)	$C_{26}H_{23}Cl_2NO_3$ (468.4)	3150, 1700, 1680, 1650	2.40 (s, 6H); 3.00 (s, 2H); 3.2 (m, 2H); 4.00 (q, 1H); 6.9-7.8 (m, 11H); 8.2 (q, 1H)
		+						
		6c	4-H_3C	11	see above	—	—	
m-xylene **(2d)**	r.t./3	**7d**	2,4-di-H_3C	69	190° (C_6H_6)	$C_{28}H_{27}Cl_2NO_3$ (496.4)	3200, 1700, 1685, 1650	—

[a] Satisfactory microanalyses obtained: C ±0.45, H ±0.37, N ±0.38; exceptions: **6b**: C, +0.54; **6c**, C +0.52, **7d**, +0.56.

ine (2.2 ml) and then with thionyl chloride (1.8 ml) at 0 °C for 30 min. The benzene solution of the acid chloride is decanted from the solid cake formed. The cake is pulverised, extracted with dry benzene (30 ml) and the benzene solutions combined. The benzene solution of the acid chloride is added drop-wise to a solution of glycine (1.5 g, 0.02 mol) in aqueous potassium hydroxide solution (5%, 20 ml) with vigorous shaking and the mixture is then allowed to stand at room temperature for 1 h. The mixture is acidified with dilute hydrochloric acid (5 ml), the organic layer is separated, washed with water (100 ml), and dried with sodium sulphate. The solvent is distilled and the residue is recrystallised from benzene; yield: 4.7 g (79%); m.p. 136 °C.

$C_{12}H_9Cl_2NO_4$	calc.	C 47.82	H 2.86	N 4.78
(302.2)	found	47.68	2.98	4.63

2-[3-(3,4-Dichlorophenyl)-3-oxopropenyl]-5-oxo-4,5-dihydro-1,3-oxazole (**5**): A solution of the acryloylglycine (2 g, 0.007 mol) in freshly distilled acetic anhydride (20 ml) is heated at 100 °C for 1 h, then concentrated, and cooled. The product **5** is isolated by filtration; yield: 1.5 g (83%); m.p. 111 °C (from 60-80 °C petroleum ether).

$C_{12}H_7Cl_2NO_3$	calc.	C 50.70	H 2.46	N 4.92
(284.2)	found	51.13	2.67	5.33

I.R. (KBr): ν = 1760 (C=O of azlactone); 1670 (C=O); 1630 (C=N) cm^{-1}.

N-Aroylmethyl-β-(3,4-dichlorobenzoyl)-acrylamides 6; General Procedure:

A stirred solution of **5** (2.8 g, 0.01 mol) in an aromatic solvent **2** (50 ml) is treated with anhydrous aluminium chloride (4.0 g, 0.03 mol) portion-wise. Stirring is continued at room temperature for 10 h. The mixture is then added to concentrated hydrochloric acid (20 ml)/ice (100 g). The organic layer is separated, washed with water (250 ml), and excess aromatic solvent is removed by steam distillation. The separated solid is recrystallised from a suitable solvent to give the products **6** and **7** (Table).

N-(Aroylmethyl)-2-aryl-3-(3,4-dichlorophenyl)-propanamides 7; General Procedure:

Aluminium chloride (8.0 g, 0.06 mol) is added to a vigorously stirred solution of **5** (2.8 g, 0.01 mol) in an aromatic solvent **2** (50 ml). The solution is heated at 100 °C for 10 h and then allowed to stand at room temperature overnight. The mixture is added to concentrated hydrochloric acid (40 ml)/ice (200 g). The organic layer is washed with water (250 ml), excess aromatic solvent removed by steam distillation. The residual organic material is extracted with ether (300 ml) and the extract dried with anhydrous sodium sulphate. The solvent is distilled and the residue fractionally crystallised from suitable solvents to give **7** and **6** (Table).

2-(2,4-Dimethylphenyl)-4-(3,4-dichlorophenyl)-4-oxobutanoic Acid (9):

A solution of **7d** (2.0 g, 0.004 mol) in glacial acetic acid (10 ml) and concentrated hydrochloric acid (10 ml) is heated under reflux for 4 h. The mixture is poured on to ice (50 g). The solid which separates is filtered; yield: 0.8 g (53%); m.p. 179 °C (Ref.[4], m.p. 179 °C).

Friedel-Crafts Alkylation of *m*-Xylene (2d) with 4-(3,4-Dichlorophenyl)-4-oxo-2-butenoic Acid (8):

Method A: A solution of **8** (2.4 g, 0.01 mol) in *m*-xylene (**2d**; 50 ml) is saturated with dry hydrogen chloride gas and aluminium chloride (5.4 g, 0.04 mol) is added. Vigorous evolution of hydrogen chloride occurs and a yellow paste precipitates. The temperature of the mixture is maintained at 20-25 °C and stirring is continued for 15 h. The mixture is added to concentrated hydrochloric acid (40 ml)/ice (200 g). The organic layer is washed with water (200 ml), excess **2d** is removed by steam distillation, and the residue is recrystallised from benzene to give **9**; yield: 2.5 g (70%); m.p. 179 °C (Ref.[4], m.p. 179 °C).

Method B: A solution of **7** (2.4 g, 0.01 mol) in m-xylene (50 ml) is treated with aluminium chloride (5.4 g, 0.04 mol) and the mixture is heated at 100°C for 10 h. The mixture is then treated as described above to give **9**; yield: 2.4 g (70%).

Received: December 8, 1980
(Revised form: March 9, 1981)

---

[1] A. M. Islam, I. B. Hannout, L. M. Souka, H. Aref, *Egypt. J. Chem.* **20**, 473 (1977).

[2] M. A. El-Hashash, M. A. Sayed, *Egypt. J. Chem.* **21**, 115 (1978).

[3] M. A. El-Hashash, M. A. Hassan, M. A. Sayed, *Pak. J. Sci. Ind. Res.* **20**, 336 (1977).

[4] M. A. El-Hashash, G. Hosni, M. El-Kady, *Rev. Roum. Chim.* **24**, 839 (1979).

[5] M. A. El-Hashash, M. El-Kady, M. M. Mohamed, *Ind. J. Chem.* [B] **18**, 136 (1979).

[6] A. Sammour, A. A. Afify, M. M. Abd-Allah, E. A. Soliman, *Acta Chim. Acad. Sci. Hung.* **85**, 455 (1975).

[7] A. M. Islam, A. M. Khalil, J. J. Abdel-Gawad, *Aust. J. Chem.* **26**, 827 (1973).

0039-7881/81/1032-0801 $ 03.00