# Behaviour of some 2(3*H*)-furanones bearing a pyrazolyl group as alkylating agents

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5-Aryl-3-(1,3-diphenylpyrazol-4-ylmethylene)-2(3*H*)-furanones (**1a–c**) were prepared by condensing 1,3-diphenylpyrazole-4-carboxaldehyde with 3-aroylpropionic acids in the presence of *N,N*-dimethyl(chlorosulfinyloxy)methaniminium chloride as a cyclodehydrating agent. The reactions of these furanones with anhydrous aluminium chloride in benzene, toluene and anisole led to the formation of 4,4-diaryl-1-(1,3-diphenylpyrazol-4-yl)buta-1,3-diene-2-carboxylic acids (**6**) as mixtures of two geometrical (*E,E*- and *E,Z*-) stereoisomers. The unfavoured intramolecular alkylation of **1a–c** compared with other furanones is discussed using Hyper Chem Professional (7) $AM_1$ calculations.

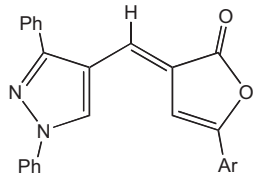
**Keywords**: 2(3*H*)-furanones, pyrazoles, dienes, electrophilic alkylation

2(3*H*)-Furanones represent an important type of furanones. Unlike the other two types, 2(5*H*)-and 3(2*H*)-furanones, the 2(3*H*)-compounds are characterised by facile opening of the lactone ring by both nucleophilic and electrophilic reagents. From this point of view, 2(3*H*)-furanones are considered as versatile synthons for a variety of synthetically and biologically important heterocyclic systems *viz.* pyrrolones,[1,2] pyridazinones,[3,4] oxadiazoles,[5,6] pyrazoles[7] and isothiazolones.[8,9]

In this investigation, some 2(3*H*)-furanones carrying a pyrazole moiety (**1a–c**) are synthesised with a view to a study their behaviour as alkylating agents.

## Results and discussion

1,3-Diphenylpyrazole-4-carboxaldehyde[10] condenses with 3-aroylpropionic acids, using *N,N*-dimethyl(chlorosulfinyloxy) methaniminium chloride (prepared by reacting thionyl chloride with *N,N*-dimethylformamide in benzene) as a cyclodehydrating agent,[11] to give 5-aryl-3-(1,3-diphenylpyrazol-4-ylmethylene)-2(3*H*)-furanones (**1a–c**). The structure of the latter products is inferred from their analytical as well as spectroscopic data (*cf.* Experimental section).

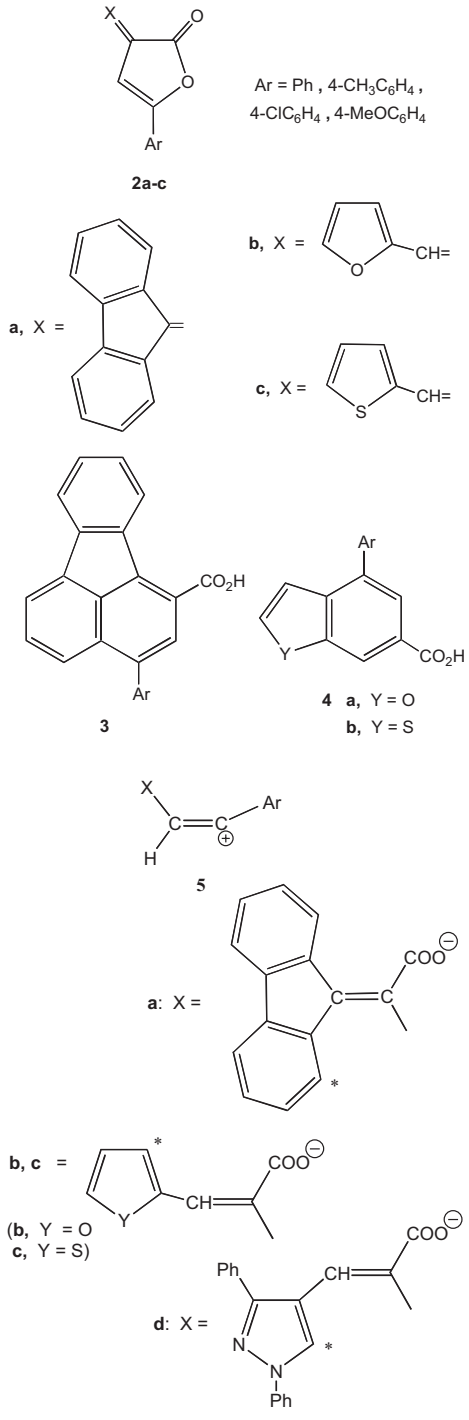


**1a-c**

**a**, Ar = Ph
**b**, Ar = 4-$ClC_6H_4$
**c**, Ar = 4-$MeOC_6H_4$

The behaviour of some 3-aryl and heteroarylmethylene-2(3*H*)-furanones (**2**) as alkylating agents has previously been investigated by our research group. It was found that when the furanones **2a–c** (X = 9-fluorenylidene, 2-furylmethylene and 2-thienylmethylene) were allowed to react with aluminium chloride in excess benzene, fluoranthenecarboxylic acids **3**,[12] benzofuran[13] and benzothiophene[14] carboxylic acids **4**, respectively, were obtained. The formation of these acids was explained on the basis of intramolecular alkylation reactions. The furanones are firstly converted, by alkyl–oxygen ring cleavage, into resonance stabilised carbocations **5a–c** which on electrophilic attack at the *ortho* position (∗) afforded **3** and **4**.

It was of interest to the authors to investigate the behaviour of the newly synthesised pyrazolylmethylenefuranones **1** as alkylating agents. Cyclisation to the pyrazole 5-position (∗ in **5d**) appeared to be a possibility.



Ar = Ph , 4-$CH_3C_6H_4$ , 4-$ClC_6H_4$ , 4-$MeOC_6H_4$

**2a-c**

**a**, X =

**b**, X =

**c**, X =

**3**

**4** **a**, Y = O
**b**, Y = S

**5**

**a**: X =

**b**, **c** =

(**b**, Y = O
**c**, Y = S)

**d**: X =

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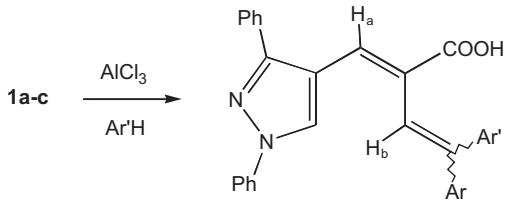


**6a-h**

| 6 | Ar | Ar' |
|---|---|---|
| **a** | $C_6H_5$ | $C_6H_5$ |
| **b** | 4-$CH_3OC_6H_4$ | 4-$CH_3OC_6H_4$ |
| **c** | $C_6H_5$ | 4-$CH_3OC_6H_4$ |
| **d** | $C_6H_5$ | 4-$CH_3C_6H_4$ |
| **e** | 4-$CH_3OC_6H_4$ | 4-$CH_3C_6H_4$ |
| **f** | 4-$ClC_6H_4$ | $C_6H_5$ |
| **g** | 4-$ClC_6H_4$ | 4-$CH_3C_6H_4$ |
| **h** | 4-$ClC_6H_4$ | 4-$CH_3OC_6H_4$ |

We found that the furanones **1** reacted with $AlCl_3$ in excess benzene, toluene, or anisole to give the butadienecarboxylic acids **6**. The structures of these acids was inferred from (i) analytical data and mass spectroscopic data indicated the incorporation of phenyl group in the acids **6a,f**, the tolyl group in **6d,e,g** and the anisyl group in **6b,c,h**; (ii) the IR spectra of these acids, showed broad bands in the region 2,800–3,500 $cm^{-1}$ characteristic of the hydrogen bonded OH moiety of the carboxyl group, as well as a band at 1678 $cm^{-1}$ for the carbonyl of the carboxylic acid groups (*cf.* Experimental section).

The $^1H$ NMR spectra of compounds **6c–h** showed two singlets for the olefinic proton $H_b$, as well as two singlets for $OCH_3$ protons in case of **6c,e,h** and two singlets for $CH_3$ protons in case of **6d,e,g**. This revealed the existence of compounds **6c–h** as a mixture of two geometrical (*E*,*E*)- and (*E*,*Z*)-stereoisomers in which the latter predominate. The lower ratio as well as the deshielding of the olefinic proton $H_b$ in case of (*E*,*E*)-isomer as compared with the (*E*,*Z*)-counterpart can be rationalised in terms of steric considerations and the ring current of the more activated aryl groups, respectively.

The formation of the acids **6** can undoubtedly be explained on the basis of an intermolecular alkylation reaction. The carbocation **5d** formed via an alkyl–oxygen cleavage of the furanone **1** attacks the aromatic solvent (benzene, toluene or anisole) to afford **6**.

In the presence of toluene or anisole in the reaction medium, intermolecular alkylation is not unexpected. It was previously reported[15] that in the reaction of the furanones **2a** with aluminium chloride; changing benzene to the more effective nucleophiles toluene or anisole changed the mode of reaction from intra- to inter-molecular. In our study here, it is evident that benzene, which in the previous studies served only as a solvent, has participated in the reaction. Therefore, the pyrazolyl furanones **1** are not favourable for the intramolecular mode of alkylation. This behaviour was further supported by attempts to carry out the reaction of the furanones **1** with aluminium chloride in tetrachloroethane and nitrobenzene as solvents; the reactions failed to give any product and the unreacted furanones were isolated.

We sought to verify the unreactivity of the pyrazolyl furanones **1** in the intramolecular alkylation mode by applying the Hyper Chem Professional (7) $AM_1$ calculations[16] to the intermediate carbocations **5**. Intramolecular alkylation may be regarded as an intramolecular charge transfer between the interacting positions in the molecule. The results of the calculations are listed in Table 1.

In agreement with the experimental results, Table 1 indicates that intramolecular alkylation in **5d** is much less favourable than in the other carbocations **5a–c**. This is due to the lower value of HOMO at C* and the lower value of LUMO at the attacking carbocationic centre. Moreover, the much lower magnitude of the charge density at C* renders electrophilic attack on this carbon very difficult.

**Table 1** Frontier coefficients of the reactive sites in **5a–d** with charge density on C*

| No. | HOMO (C*) eV | LUMO ($C^+$) eV | Charge density (C*) |
|---|---|---|---|
| **5a** | –8.079 | –1.493 | –0.104 |
| **5b** | –9.079 | –1.571 | –0.175 |
| **5c** | –8.544 | –1.728 | –0.145 |
| **5d** | –7.951 | –1.459 | –0.073 |

## Experimental

Melting points were measured on an electrothermal melting point apparatus. Elemental analyses were carried out at the Microanalytical Unit, Cairo University. IR spectra were measured on a Unicam SP-1200 spectrometre using KBr wafer technique. $^1H$ NMR spectra were measured in DMSO-$d_6$ or $CDCl_3$ on a Varian Plus instrument (300 MHz). Mass spectra were recorded on a Shimadzu GC-MS QP 1000 EX instrument operating at 70 eV.

1,3-Diphenylpyrazole-4-carboxaldehyde was prepared according to ref. 10.

*5-Aryl-3-(1,3-diphenylpyrazol-4-ylmethylene)-2(3H)-furanones* (**1a–c**)

(i) *(Chlorosulfinyloxy)-N,N-dimethylmethaniminium chloride* (the cyclodehydrating reagent): 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-aroylpropionic acid (10 mmole) in 25 ml dichloromethane at 0 °C, the cyclodehydrating agent (10 mmole) prepared in the above step was added. After the mixture had been stirred for 15 minutes the aldehyde (1,3-diphenylpyrazole-4-carboxaldehyde)[10] (10 mmole) was added followed dropwise by triethylamine (30 mmole) in dichloromethane (15 ml). The resulting mixture was stirred at room temperature for 5 hours. 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 from benzene.

*5-Phenyl compound* **1a**: M.p. 229–230 °C, 80 % yield. IR: $\nu_{max}$ 1749 (C=O), 1626 (C=N), 1595 $cm^{-1}$ (C =C). $^1H$ NMR (DMSO-$d_6$): δ 7.21 (s, 1H, $H_a$), 7.45–7.68 (m, 12H, ArH), 7.88 (d, 2H, $H_b$, $J$ = 6.6 Hz), 8.07 (d, 2H, $H_c$, $J$ = 7.8 Hz), 9.26 (s, 1H, $H_d$). EI-MS: *m/z* (%) 390 ($M^+$, 77), 258 (42), 257 (67), 105 (70), 77 (base), 51 (38). Anal. Calcd for $C_{25}H_{18}N_2O_2$: C, 80.00; H, 4.62; N, 7.18. Found: C, 80.12; H, 4.60; N, 7.12 %.

*5-(4-Chlorophenyl) compound* **1b**: M.p. 272–274 °C, 76 % yield. IR: $\nu_{max}$ 1747 (C=O), 1626 (C=N), 1598 $cm^{-1}$ (C =C). $^1H$ NMR (DMSO-$d_6$): δ 7.23 (s, 1H, $H_a$), 7.57–7.71 (m, 11H, ArH), 7.88 (d, $H_c$, $J$ = 8.7 Hz), 8.06 (d, 2H, $H_e$, $J$ = 7.1 Hz), 9.26 (s,1H, $H_d$). Anal. Calcd. for $C_{25}H_{17}ClN_2O_2$: C, 73.58; H, 4.00; N, 6.60. Found: C, 73.52; H, 4.01; N, 6.15 %.

*5-(4-Methoxyphenyl compound* **1c**: M.p. 238–240 °C, 72 % yield. IR: $\nu_{max}$ 1747 (C=O), 1627 (C=N), 1598 $cm^{-1}$ (C =C). $^1H$ NMR (DMSO–$d_6$): δ 3.84 (s, 3H, $OCH_3$), 7.08 (s, 1H, $H_a$), 7.16 (d, 2H, $H_e$, $J$ = 8.7 Hz), 7.44–7.69 (m, 9H, ArH), 7.08 (d, 2H, $H_b$, $J$ = 9.0 Hz), 8.09 (d, 2H, $H_c$, $J$ = 8.7 Hz), 9.21 (s, 1H, $H_d$). Anal. Calcd for $C_{26}H_{20}N_2O_3$: C, 77.14; H 4.76; N, 6.67. Found: C, 77.12; H, 4.65; N, 6.63 %.

*4,4-Diaryl-1-(1,3-diphenylpyrazol-4-yl)buta-1,3-diene-2-carboxylic acids* (**6a–h**)

To a stirred mixture of anhydrous $AlCl_3$ (0.03 mole) in dry benzene, toluene or anisole (100 ml), a solution of the furanone (**1**) 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 formed was filtered off, dissolved in sodium

carbonate solution (25 ml; 20 %), cooled well, and reprecipitated by dropwise addition of conc. HCl. The solid product obtained was recrystallised from the solvent specified.

The same product, **6c**, was obtained from the reaction of **1a** in anisole and of **1c** in benzene.

*Ar = Ar′ = Ph* (**6a**): Yellowish white crystals, m.p. 258–259 °C (ethanol), 65 % yield. IR: $\nu_{max}$ 2800–3450 (OH), 1678 (C=O), 1622 (C=N), 1599 $cm^{-1}$ (C =C). $^1H$ NMR (DMSO-$d_6$): δ 6.48 (s, 1H, $H_a$), 6.69–7.52 (m, 19H, ArH), 7.87 (d, 2H, $H_c$, *J* = 7.8 Hz), 8.56 (s, 1H, $H_b$).EI-MS: *m/z* (%) 468 ($M^{+\cdot}$, 54), 467 (36), 424 (31), 420 (30), 304 (37), 303 (37), 259 (69), 258 (base), 257 (58), 77 (71). Anal. Calcd for $C_{32}H_{24}N_2O_2$: C, 82.05; H, 5.13; N, 5.98. Found: C, 82.19; H, 5.12; N, 6.12 %.

*Ar = Ar′ = p-MeOC$_6$H$_4$* (**6b**): Yellow crystals, m.p. 250–252 °C (ethanol), 75 % yield. IR: $\nu_{max}$ 2850–3425 (OH), 1675 (C=O), 1605 (C=N), 1585 $cm^{-1}$ (C =C). $^1H$ NMR (DMSO-$d_6$): δ 3.59 (s, 3H, $OCH_3$), 3.76 (s, 3H, $OCH_3$), 6.72–7.52 (m, 17H, ArH), 7.76 (d, 2H, $H_c$, *J* = 7.8 Hz), 8.50 (s, 1H, $H_b$). EI-MS: *m/z* (%) 530 ($M^+$ + 2, 39), 529 (88), 528 ($M^+$, 14), 485 (50), 484 (base), 308 (76), 77 (44). Anal. Calcd for $C_{34}H_{28}N_2O_4$: C, 77.27; H, 5.30; N, 5.30. Found: C, 77.52; H, 5.34; N, 5.28 %.

*Ar = Ph, Ar′ = p-MeOC$_6$H$_4$* (**6c**): Yellow crystals, m.p. 218–220 °C (ethanol), 75 % yield. IR: $\nu_{max}$ 2845–3335 (OH), 1676 (C=O), 1626 (C=N), 1598 $cm^{-1}$ (C =C). $^1H$ NMR (DMSO-$d_6$) (*E,Z*- 55 %): δ 3.59 (s, 3H, $OCH_3$), 6.57 (s, 1H, $H_a$), 6.73–7.51 (m, 18H, ArH), 7.76 (d, 2H, $H_c$, *J* = 7.2 Hz), 8.58 (s, 1H, $H_b$). (*E,E*- 45 %): δ 3.76 (s, 3H, $OCH_3$), 8.60 (s, 1H, $H_b$). EI-MS: *m/z* (%) 453 ($M^{+\cdot}$-$CO_2$, base), 278 (44), 77 (97). Anal. Calcd for $C_{33}H_{26}N_2O_3$: C, 79.52; H, 5.22; N, 5.62. Found: C, 79.39; H, 5.20; N, 5.60 %.

*Ar = Ph, Ar′ = p-CH$_3$C$_6$H$_4$* (**6d**): Yellow crystals, m.p. 259–260 °C (benzene/ethanol), 60 % yield. IR: $\nu_{max}$ 2830–3415 (OH), 1703 (C=O), 1620 (C=N), 1603 $cm^{-1}$ (C =C). $^1H$ NMR ($CDCl_3$) (*E, Z*- 55 %): δ 2.31 (s, 3H, $CH_3$), 6.48 (s, 1H, $H_a$), 6.69–7.52 (m, 18H, ArH), 7.76 (d, 2H, $H_c$, *J* = 7.8 Hz), 8.58 (s, 1H, $H_b$); (*E,E*- 45 %): δ 2.34 (s, 3H, $CH_3$), 8.60 (s, 1H, $H_b$). EI-MS: *m/z* (%) 484 ($M^{+\cdot}$ + 2, 48), 483 (39), 440 (70), 439 (54), 407 (48), 406 (44), 304 (38), 303 (44), 259 (36), 258 (58), 257 (47), 234 (40), 233 (68), 220 (41), 135 (35), 121 (96), 77 (base), 51 (65), 50 (31). Anal. Calcd for $C_{32}H_{24}N_2O_2$: C, 82.16; H 5.39; N, 5.81. Found: C, 82.23; H, 5.37; N, 5.87 %.

*Ar = p-MeOC$_6$H$_4$, Ar′ = p-CH$_3$C$_6$H$_4$* (**6e**): Yellowish white crystals, m.p. 270–272 °C (benzene/ethanol), 68 % yield. IR: $\nu_{max}$ 3100–3424 (OH), 1703 (C=O), 1620 (C=N), 1600 $cm^{-1}$ (C =C). $^1H$ NMR ($CDCl_3$) (*E,Z*- 50 %): δ 2.19 (s, 3H, $CH_3$), 3.59 (s, 3H, $OCH_3$), 6.48 (s, 1H, $H_a$), 6.69–7.52 (m, 17H, ArH), 7.76 (d, 2H, $H_c$, *J* = 7.8 Hz), 8.56 (s, 1H, $H_b$); (*E,E*- 50 %): δ 2.27 (s, 3H, $CH_3$), 3.76 (s, 3H, $OCH_3$), 8.58 (s, 1H, $H_b$) Anal. Calcd for $C_{34}H_{28}N_2O_3$: C, 79.69; H 5.47; N, 5.47. Found: C, 79.73; H, 5.41; N, 5.40 %.

*Ar = p-ClC$_6$H$_4$, Ar′ = Ph* (**6f**): Yellowish white crystals, m.p. 225–227 °C (benzene/ethanol), 70 % yield. IR: $\nu_{max}$ 2850–3300 (OH), 1678 (C=O), 1625 (C=N), 1599 $cm^{-1}$ (C =C). $^1H$ NMR (DMSO-$d_6$) (*E,Z*- 60 %): δ 6.57 (s, 1H, $H_a$), 6.73–7.51 (m, 18H, ArH), 7.76 (d, 2H, $H_c$, *J* = 7.2 Hz), 8.58 (s, 1H, $H_b$). (*E,E*- 40 %): δ 8.60 (s, 1H, $H_b$). EI-MS: *m/z* (%) 460 (5), 458 (15.2) ($M^+$-$CO_2$), 424 (42), 257 (96), 139 (55), 111 (41), 77 (base), 51 (45). Anal. Calc. for $C_{32}H_{23}ClN_2O_2$: C, 76.49; H 4.58; N, 5.57. Found: C, 76.52; H, 4.54; N, 6.01 %.

*Ar = p-ClC$_6$H$_4$, Ar′ = p-CH$_3$C$_6$H$_4$* (**6 g**): Yellow crystals, m.p. 265–266 °C (benzene/ethanol), 62 % yield. IR: $\nu_{max}$ 2900–3450 (OH), 1679 (C=O), 1622 (C=N), 1595 $cm^{-1}$ (C =C). $^1H$ NMR ($CDCl_3$) (*E, Z*- 70 %): δ = 2.19 (s, 3H, $CH_3$), 6.60 (s, 1H, $H_a$), 6.74–7.51 (m, 17H, ArH), 7.77 (d, 2H, $H_c$, *J* = 7.8 Hz), 8.58 (s, 1H, $H_b$). (*E,E*- 30 %): δ = 2.27 (s, 3H, $CH_3$), 8.60 (s, 1H, $H_b$) Anal. Calc. for $C_{33}H_{25}ClN_2O_2$: C, 76.74; H 4.84; N, 5.43. Found: C, 76.82; H, 4.84; N, 5.39 %.

*Ar = p-ClC$_6$H$_4$, Ar′ = p-MeOC$_6$H$_4$* (**6 h**): Yellow crystals, m.p. 230–231 °C (ethanol), 81 % yield. IR: $\nu_{max}$ 2837–3448 (OH), 1676 (C=O), 1602 (C=N), 1590 $cm^{-1}$ (C =C). $^1H$ NMR ($CDCl_3$) (*E, Z*- 80 %): δ 3.59 (s, 3H, $OCH_3$), 6.59 (s, 1H, $H_a$), 6.74–7.51 (m, 18H, ArH), 7.77 (d, 2H, $H_c$, *J* = 7.8 Hz), 8.58 (s, 1H, $H_b$) (*E,E*- 20 %): δ 3.76 (s, 3H, $OCH_3$), 8.60 (s, 1H, $H_b$). EI-MS: *m/z* (%) 534 (26), 532 (62) ($M^+$) 490 (39), 489 (38), 488 (42), 314 (30), 312 (77), 220 (80), 219 (31), 77 (base), 51 (31). Anal. Calcd for $C_{33}H_{25}ClN_2O_3$: C, 74.73; H 4.70; N, 5.26. Found: C, 74.51; H, 4.73; N, 5.23 %.

*Reaction of the furanones* **1a-c** *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.

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