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Proceeding Paper

Synthesis of New Representatives of Push-Pull Enamines 5-Aryl-3-((dimethylamino)methylene)furan-2(3*H*)-Ones †

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Abstract: The conditions for the synthesis of dimethylaminomethylene derivatives were selected based on the interaction of arylfuran-2(3*H*)-ones and dimethylformamide dimethylacetal (DMA-DMF), proceeding through the methylene active unit of the furanone ring. The influence of the used solvent and the type of activation on the reaction rate and product yields was established. Using NMR spectroscopy and the one-dimensional version of NOESY1D with selective excitation of protons, it was revealed that these systems exist in the form of an *E*-configuration.

Keywords: dimethylformamide dimethylacetal; furan-2(3*H*)-ones; dimethylaminomethylene derivatives; physicochemical methods

1. Introduction

Furan-2(3*H*)-one is a promising heterocycle that has high chemical potential and acts as an easily accessible and platform starting material for the synthesis of new series of compounds. The furan-2(3*H*)-one ring system is the main element of the skeleton of antitumor drugs [1–4], compounds with antioxidant [5] and antibacterial effects [6–8]. One of the most important tasks of organic chemistry is the development of new preparative methods for the synthesis of compounds that are capable of further modifications, leading to a variety of heterocyclic structures and containing pharmacophore fragments. Such compounds include dimethylaminomethylene derivatives, which have high prospects in the design of bioactive compounds that have antitumor [9], antioxidant [10] activity and are used as antibiotics [11].

Dimethylaminomethylenefuran-2(3*H*)-ones can be classified as highly effective synthons due to the presence of several active reaction centers, as well as the pronounced push-pull nature of the C=C bond, due to the presence of the carbonyl group of the furan-2(3*H*)-one fragment conjugated with the amino group. However, information on methods of preparation and properties of these systems is missing in the literature, which determines the relevance of searching for methods for synthesizing these compounds.

The most well-known synthetic reagent in the literature for the generation of enamine derivatives is dimethylformamide dimethyl acetal (DMF-DMA), the high reactivity of which is explained by the presence of methoxy groups that provide a partially positive charge on the carbon atom. Consequently, the DMF-DMA reagent can easily enter into condensation reactions with various functional groups of organic compounds, most often of which are methylene, methyl and amino groups, and it is also widely used as a one-carbon synthon for the construction of carbon skeletons [12–20].

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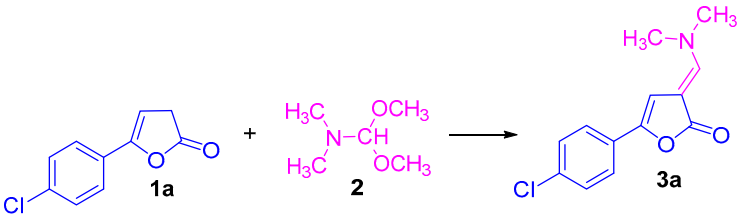
2. Results and Discussion

2.1. Synthesis of 5-Aryl-substituted 3-((dimethylamino)methylene)furan-2(3H)-Ones

We have investigated the possibility of introducing a dimethylaminomethylene fragment into the molecule of 5-arylfuran-2(3*H*)-ones. The conditions for the synthesis of dimethylaminomethylene derivatives of furan-2(3*H*)-one were optimized using the model reaction of 5-(4-chlorophenyl)-furan-2(3*H*)-one **1a** with DMF-DMA **2** as an example (Scheme 1); the reagents were used in a molar ratio of 1:1 (Table 1).

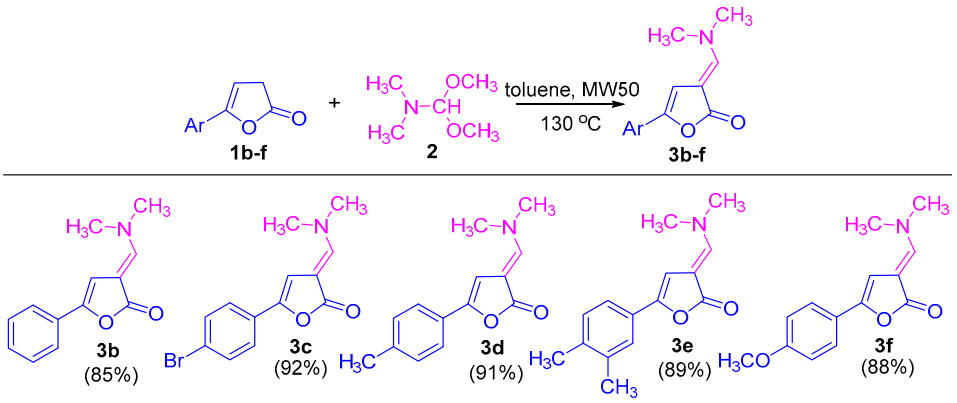


Scheme 1. Optimization of conditions for the interaction of 5-(4-chlorophenyl)furan-2(3*H*)-one and DMF-DMA**.**

Table 1. Optimization of reaction conditions for the synthesis of 5-(4-chlorophenyl)-3-((dimethylamino)methylene)furan-2(3*H*)-one **3a**.

Entry	Solvent	Temperature, °C	Time (min)	Yield, %
1	EtOH	78	180	50
2	i-PrOH	82	178	50
3	MeCN	81	150	50
4	1,4-Dioxane	101	160	61
5	Benzene	80	173	57
6	Toluene	110	110	70
7	Solvent-free	153	-	-
8	Toluene	115	25	75
9	Toluene	130	6	90
10	Toluene	150	-	-

When the reaction mixture is refluxed in an EtOH environment, it leads to the target product within 3 h with a yield of 50%; when using the more polar solvent acetonitrile, the reaction time is reduced to 2.5 h, however, the yield of the product does not change. Under these conditions, we tested non-polar solvents—benzene and toluene. The best results were obtained in toluene. Also, carrying out the reaction under solvent-free conditions in a twofold excess of DMF-DMA was not successful. Further attempts to increase the yield of the desired product and reduce the conversion time were achieved using a Monowave 50 pressurized vessel reactor (Anton Paar). When carrying out the transformation at 120 °C in toluene, the reaction time was reduced to 25 min with a yield of 75%; increasing the temperature to 130 °C allowed us to carry out the reaction for 6 min with a yield of 90%. However, a subsequent increase in temperature did not give the desired results and tarring of the reaction mixture was observed. Thus, these conditions were chosen as optimal for research (Scheme 2).



Scheme 2. General scheme for the synthesis of 3-dimethylaminomethylenefuran-2(3*H*)-ones **3b–f.**

The advantages of this type of activation of the reaction mixture are: new reaction pathways, i.e., by varying the heating time and temperature, one can observe the formation of various intermediate reaction products; significant reduction in transformation time, increased product yields, minimized solvent consumption and the ability to carry out reactions without the use of catalysts, which meets the principles of "green chemistry". The literature provides isolated information on the study of the features of carrying out various chemical transformations using a reactor of this type, which determines the relevance of research in this area.

The use of a sealed vessel reactor allowed us to monitor and analyze conditions inside the vial (Figure 1).

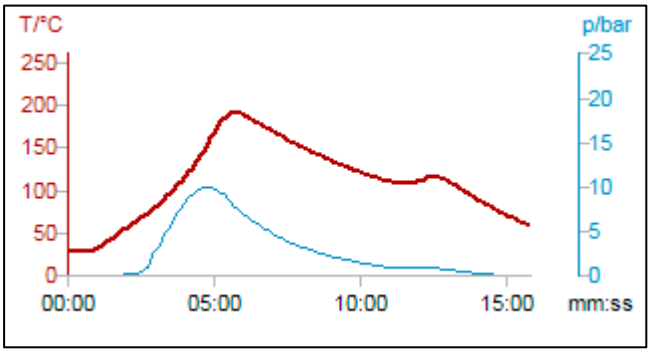


Figure 1. Temperature (red) and pressure (blue) inside the vial during the synthesis reaction of compound 3a, according to the built-in sensors of the sealed vessel reactor.

The temperature curve smoothly increases to 50 °C, which corresponds to the process of dissolution of the initial components, followed by a sharp increase to 191 °C, significantly exceeding the initially set temperature value. This indicates an exothermic reaction occurring with the formation of 5-(4-chlorophenyl)-3-((dimethylamino)methylene)furan-2(3*H*)-one. An increase in temperature above the boiling point of toluene (130 °C versus 110 °C) gives us the opportunity to enhance the interaction due to the formation of a gaseous water-toluene azeotrope, which is shown by an increase in pressure up to 10 bar (Figure 1).

2.2. Structure of 3-Dimethylaminomethylene Derivatives of Furan-2(3H)-Ones ***3a–f***

The structures of the new compounds were determined by spectroscopic methods (^{1}H, ^{13}C NMR, HMBC, HSQC, NOESY1D) and elemental analysis data. Phenyldimethylaminomethylenefuran-2(3*H*)-ones showed ^{1}H and ^{13}C NMR data sets consistent with the proposed structures. Compounds **3a–f** showed ^{1}H NMR chemical shifts for the protons of the methyl group NMe_2 in the form of one singlet in the range of 3.30–3.33 ppm. Signals

of vinyl protons of the furan-2(3*H*)-one ring were observed in the range of 6.83–7.09 ppm, protons belonging to the exocyclic double bond C=C appeared at 7.19–7.28 ppm. The resulting structures were found to exist as the *E*-isomer, the configuration of which around the C=C bond was confirmed using a one-dimensional variant of NOESY1D under selective excitation. It was shown that there is no spatial correlation between the vinyl proton of the furan-2(3*H*)-one fragment and the proton at the C=C bond, which indicates in favor of the *E*-configuration.

3. Material and Methods

3.1. Physical Measurements

The ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra in acetone-d_6 were recorded with a Varian (Agilent) 400 spectrometer (Agilent Technologies, Santa Clara, California, USA), and the internal standard was TMS. Chemical shifts (δ) are reported in ppm. Elemental analysis was performed on a CHNS analyzer "Elementar Vario MICRO cube" (Elementar Analysensysteme GmbH, Hanau, Germany). Melting points were determined on a *Stuart*™ SMP10 melting point apparatus (Cole-Parmer, Beacon Road, Stone, Staffordshire, ST15 OSA, UK). The progress of the reaction and the purity of the synthesized compounds were monitored by TLC on ALUGRAM®® SIL G UV254 plates (MACHEREY-NAGEL GmbH & Co. KG, Düren, Germany), a hexane-ethyl acetate-acetone (2:2:1) mixture was the eluent.

*3.2. Synthesis and Characterization of Compounds **3a–f***

A mixture of 1 mmol of the corresponding 5-arylfuran-2(3*H*)-one **1a–f** and 1 mmol of DMF-DMA 2 in 5 mL of toluene was placed in a Monowave 50 Anton Paar sealed vessel reactor and heated at 130 °C for 6 min. The crystals that precipitated during cooling were washed with cold toluene, recrystallized from ethanol, and dried.

*5-(4-(Chlorophenyl)-3-((dimethylamino)methylene)furan-2(3H)-one **3a***

Yellow crystals (ethanol), yield 0.33 g (90%), mp 210–211 °C; ^{1}H NMR (400 MHz, acetone-d_6): δ 3.33 (s, 6H, CH_3), 7.07 (s, 1H, Fu), 7.28 (s, 1H, =CH), 7.38 (d, *J* = 8.0 Hz, 2H, Ar), 7.60 (d, *J* = 8 Hz, 2H, Ar); ^{13}C NMR (100 MHz, acetone-d_6): δ 45.67, 95.22, 101.45, 124.53, 128.61, 131.48, 143.67, 147.56, 170.03 (C=O). Anal. calcd. for $C_{13}H_{12}ClNO_2$: C: 62.53%; H: 4.84%; N: 5.61%; Cl: 14.20%; Found: C: 62.75%; H: 4.98%; N: 5.82%; Cl: 14.06%.

*5-Phenyl-3-((dimethylamino)methylene)furan-2(3H)-one **3b***

Yellow crystals (ethanol), yield 0.29 g (85%), mp 206–207 °C; ^{1}H NMR (400 MHz, acetone-d_6): δ 3.32 (s, 6H, CH_3), 7.01 (s, 1H, Fu), 7.21–7.25 (m, 2H, Ar+1H, =CH), 7.34–7.38 (t, 2H, Ar), 7.61 d, (*J* = 8.0 Hz, 2H, Ar); ^{13}C NMR (100 MHz, acetone-d_6): δ 95.24, 100.49, 123.07, 127.05, 128.51, 130.53, 131.09, 144.89, 147.15, 171.09 (C=O). Anal. calcd. for $C_{13}H_{13}NO_2$: C: 72.54%; H: 6.09%; N: 6.51%; Found: C: 71.99%; H: 5.87%; N: 6.02%.

*5-(4-(Bromophenyl)-3-((dimethylamino)methylene)furan-2(3H)-one **3c***

Red crystals (ethanol), yield 0.32 g (92%), mp 224–225 °C; ^{1}H NMR (400 MHz, acetone-d_6): δ 3.32 (s, 6H, CH_3), 7.09 (s, 1H, Fu), 7.28 (s, 1H, =CH), 7.50–7.55 (m, 4H, Ar); ^{13}C NMR (100 MHz, acetone-d_6): δ 38.90, 45.92, 95.08, 101.62, 119.87, 124.80, 129.73, 131.59, 143.68, 147.59, 170.83 (C=O). Anal. calcd. for $C_{13}H_{12}BrNO_2$: C: 53.08%; H: 4.11%; N: 4.76%; Br: 27.16%; Found: C: 53.43%; H: 4.28%; N: 4.31%; Br: 27.66%.

*5-(4-(Methylphenyl)-3-((dimethylamino)methylene)furan-2(3H)-one **3d***

Yellow crystals (ethanol), yield 0.32 g (91%), mp 215–216 °C; ^{1}H NMR (400 MHz, acetone-d_6): δ 2.31 (s, 3H, CH_3), 3.31 (s, 6H, CH_3), 6.93 (s, 1H, Fu), 7.22 (s, 1H, =CH), 7.18 (d, *J* = 8 Hz, 2H, Ar), 7.69 (d, *J* = 8 Hz, 2H, Ar); ^{13}C NMR (100 MHz, acetone-d_6): δ 20.54, 38.73, 45.70, 95.39, 99.61, 123.10, 127.83, 129.15, 136.6, 145.08, 146.78, 171.16 (C=O). Anal. calcd. for $C_{14}H_{15}NO_2$: C: 73.34%; H: 6.59%; N: 6.11%; Found: C: 73.72%; H: 6.92%; N: 6.65%.

*5-(3,4-(Dimethylphenyl)-3-((dimethylamino)methylene)furan-2(3H)-one **3e***

Yellow crystals (ethanol), yield 0.33 g (89%), mp 207–209 °C; ^{1}H NMR (400 HMz, acetone-d_6): δ 2.24 (d, *J* = 4 Hz, 6H, CH_3), 3.30 (s, 6H, CH_3), 6.90 (s, 1H, Fu), 7.21 (s, 1H, =CH), 7.11 (d, *J* = 8 Hz, 1H, Ar), 7.33 (d, *J* = 8 Hz, 1H, Ar), 7.40 (s, 1H, Ar); ^{13}C NMR (100 MHz, acetone-d_6): δ 18.66, 18.90, 38.73, 45.70, 95.40, 99.31, 120.74, 124.80, 128.21, 129.70, 135.61, 136.52, 145.35, 146.56, 171.18 (C=O). Anal. calcd. for $C_{15}H_{17}NO_2$: C: 74.05%; H: 7.04%; N: 5.76%; Found: C: 74.45%; H: 7.42%; N: 5.82%.

5-(4-(Methoxyphenyl)-3-((dimethylamino)methylene)furan-2(3H)-one ***3f***

Brown crystals (ethanol), yield 0.35 g (88%), mp 186–187 °C; ^{1}H NMR (400 MHz, acetone-d_6): δ 3.30 (s, 6H, CH_3), 3.81 (s, 6H, OCH_3), 6.83 (s, 1H, Fu), 6.94 (d, *J* = 8 Hz, 2H, Ar), 7.19 (s, 1H, =CH), 7.55 (d, *J* = 8 Hz, 2H, Ar); ^{13}C NMR (100 MHz, acetone-d_6): δ 38.73, 45.70, 54.68, 95.46, 98.30, 114.01, 123.32, 124.59, 159.22, 145.16, 146.33, 171.20 (C=O). Anal. calcd. for $C_{14}H_{15}NO_3$: C: 68.56%; H: 6.16%; N: 5.71%; Found: C: 69.01%; H: 6.13%; N: 5.99%.

4. Conclusions

We have developed optimal conditions for the synthesis of aryl-substituted dimethylaminomethylenefuran-2(3*H*)-ones, where arylfuran-2(3*H*)-ones and a reactive one-carbon synthone, DMF-DMA, were used as starting components. It was found that the highest yields and shorter transformation times were achieved when using a MW50 sealed vessel reactor and a non-polar solvent—toluene.

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References

1. Abdel-Hamid, H.F.; Soliman, A.; Helaly, F.M.; Ragab, S. Cytotoxic potency and induced biochemical parameters in mice serum of new furan derivatives against liver cancer cell line. *Acta Pol. Pharm.* **2011**, *68*, 499–505.
2. Sicak, Y. Design and antiproliferative and antioxidant activities of furan-based thiosemicarbazides and 1,2,4-triazoles: Their structure-activity relationship and SwissADME predictions. *Med. Chem. Res. Lett.* **2021**, *30*, 1557–1568. https://doi.org/10.1007/s00044-021-02756-z.
3. Vicidomini, C.; Cioffi, F.; Broersen, K.; Roviello, V.; Riccardi, C.; Montesarchio, D.; Capasso, D.; Di Gaetano, S.; Musumeci, D.; Roviello, G. Benzodifurans for biomedical applications: BZ4, a selective anti-proliferative and anti-amyloid lead compound. *Future Med. Chem*. **2019**, *11*, 285–302. https://doi.org/10.4155/fmc-2018-0473.
4. Kwiecien, H.; Peruzynska, M.; Stachowicz, K.; Piotrowska, K.; Bujak, I.; Kopytko, P.; Droździk, M. Synthesis and biological evaluation of 3-functionalized 2-phenyl- and 2-alkylbenzo[b]furans as antiproliferative agents against human melanoma cell line. *Bioorg. Chem*. **2019**, *88*, 102930–102941.
5. Mehta, D.K.; Das, R. Synthesis and in- vitro antioxidant activity of some new 2, 5-disubstituted-1, 3, 4-oxadiazoles containing furan moiety. *Int. J. Pharm. Sci. Res.* **2011**, *2*, 2959–2963.
6. Donlawson, C.; Nweneka, D.O.; Orie, K.; Okah, R. Synthesis and bioactivity of 1-((2-carbamoylguanidino)(furan-2-ylmethyl)urea. *Am. J. Anal. Chem.* **2020**, *11*, 280–288.
7. Xia, L.; Idhayadhulla, A.; Lee, Y.R., Wee, Y.-J.; Kim, S.H. Anti-tyrosinase, antioxidant, and antibacterial activities of novel 5-hydroxy-4-acetyl-2,3-dihydronaphtho [1,2-b]furans. *Eur. J. Med. Chem*. **2014**, *86*, 605–612. https://doi.org/10.1016/j.ejmech.2014.09.025.
8. Malladi, S.; Nadh, V.; Suresh Babu, K.; Suri Babu, P. Beni-Suef University Journal of Basic and Applied Sciences. *J. App. Sci.* **2017**, *6*, 345–353. https://doi.org/10.1016/j.bjbas.2017.08.001.
9. El-Borai, M.A.; Rizk, H.F.; Beltagy, D.M.; El-Deeb, I.Y. Microwave-assisted synthesis of some new pyrazolopyridines and their antioxidant, antitumor and antimicrobial activities. *Eur. J. Med. Chem.* **2013**, *66*, 415–422. https://doi.org/10.1016/j.ejmech.2013.04.043.

10. Farghaly, T.A.; Abdel Hafez, N.A.; Ragab, E.A.; Awad, H.M.; Abdalla, M.M. Synthesis, anti-HCV, antioxidant, and peroxynitrite inhibitory activity of fused benzosuberone derivatives. *Eur. J. Med. Chem.* **2010**, *45*, 492–500. https://doi.org/10.1016/j.ejmech.2009.10.033.
11. Lin, H.; Dai, C.; Jamison, T.F.; Jensen, K.F. A rapid total synthesis of ciprofloxacin hydrochloride in continuous flow. *Angew. Chem. Int. Ed.* **2017**, *56*, 8870–8873. https://doi.org/10.1002/anie.201703812.
12. Abu-Shanab, F.A.; Redhouse, A.D.; Thompson, J.R.; Wakefield, B.J. Synthesis of 2,3,5,6-tetrasubstituted pyridines from enamines derived from N,N-dimethylformamide dimethyl acetal. *Synthesis* **1995**, *1995*, 557–560. https://doi.org/10.1055/s-1995-3954.
13. Abu-Shanab, F.A.; Aly, F.M.; Wakefield, B.J. Synthesis of substituted nicotinamides from enamines derived from N,N-dimethylformamide dimethyl acetal. *Synthesis*. **1995**, *1995*, 923–925. https://doi.org/10.1055/s-1995-4039.
14. Abu-Shanab, F.A.; Elkholy, Y.M.; Elnagdi, M.H. Enaminones as building blocks in organic synthesis: Synthesis of new polyfunctional pyridines, condensed pyridines, and penta substituted benzene. *Synth. Commun.* **2002**, *32*, 3493–3502. https://doi.org/10.1081/scc-120014783.
15. Abu-Shanab, F.A.; Hessen, A.M.; Mousa, S.A.S. Dimethylformamide dimethyl acetal in heterocyclic synthesis: Synthesis of polyfunctionally substituted pyridine derivatives as precursors to bicycles and polycycles. *J. Heterocycl. Chem.* **2007**, *44*, 787–791. https://doi.org/10.1002/jhet.5570440406.
16. Gupton, J.T.; Krumpe, K.E.; Burnham, B.S.; Dwornik, K.A.; Petrich, S.A.; Du, K.X.; Sikorski, J.A. The application of disubstituted vinylogous iminium salts and related synthons to the regiocontrolled preparation of unsymmetrical 2,3,4-trisubstituted pyrroles. *Tetrahedron*. **1998**, *54*, 5075–5088. https://doi.org/10.1016/s0040-402000247-6.
17. Al-Mousawi, S.; John, E.; Al-Kandery, N. Studies with enaminones: Synthesis and chemical reactivity of 2-(4-dimethylamino-2-oxobut-3-enyl)-isoindole-1,3-dione and of 4-(4-dimethylamino-2-oxobut-3-enyloxy)-2H-phthalazin-1-one. *J. Heterocycl. Chem.* **2004**, *41*, 381–385. https://doi.org/10.1002/jhet.5570410312.
18. Al-Mousawi, S.; John, E.; Abdelkhalik, M.M.; Elnagdi, M.H. Enaminones as building blocks in heterocyclic syntheses: A new approach to polyfunctionally substituted cyclohexenoazines. *J. Heterocycl. Chem.* **2003**, *40*, 689–695. https://doi.org/10.1002/jhet.5570400421.
19. Bruno, O.; Schenone, S.; Ranise, A.; Bondavalli, F.; Filippelli, W.; Falcone, G.; Mazzeo, F. Antiinflammatory agents: New series of N-substituted amino acids with complex pyrimidine structures endowed with antiphlogistic activity. *Il Farmaco.* **1999**, *54*, 95–100. https://doi.org/10.1016/s0014-827x(98)00109-8.
20. Mustazza, C.; Giudice, M.R.D.; Borioni, A.; Gatta, F. Synthesis of pyrazolo [1,5-a]-, 1,2,4-triazolo [1,5-a]- and imidazo [1,2-a]pyrimidines related to zaleplon, a new drug for the treatment of insomnia. *J. Heterocycl. Chem.* **2001**, *38*, 1119–1129. https://doi.org/10.1002/jhet.5570380516.