

Knoevenagel condensation of 5-substituted furan-2-carboxaldehyde with Indan-1,3-dione

**M. I. Khalaf; A. Abdel-wahab
and F. Kandil**

Department of Chemistry, Faculty of Sciences, Damascus University, Syria.

Received 08/12/2011

Accepted 02/04/2012

ABSTRACT

A series of new heterocyclic compounds of 2-(5-substituted-furfurylidene)-Indane-1,3-dione, were prepared and identified by their melting points, Infrared, Ultraviolet, and Nuclear magnetic resonance spectra.

Key words: Knoevenagel condensation, Furfurylidene, Indan-1,3-dione.

تكاثف نوفيناجيل لبعض مشتقات الفورفورال مع الاندان-3,1-دايون

منى اسماعيل خلف و عبدو عبد الوهاب و فاروق قنديل

قسم الكيمياء - كلية العلوم - جامعة دمشق - سورية

تاريخ الإبداع 2011/12/08

قبل للنشر في 2012/04/02

الملخص

حُضرت سلسلة جديدة من المركبات الحلقية غير المتجانسة من 2 _ (5 - معوض -فورفورالدين) _
أندان 3,1 _ ديون بواسطة تكاثف مشتقات الفورفورال مع مركب الاندان 1,3_ديون، وصفت المركبات
المحضرة بتعيين درجات انصهارها وبمطيافيات IR، UV، ¹H-NMR.

الكلمات المفتاحية: تكاثف نوفيناجيل، فورفورال، فورفورالدين. اندان-3,1-ديون.

Introduction

One of the most important properties of Knoevenagel condensation from a synthetic perspective is that they offer a route to the formation of C=C bond, by which the arylidene compounds are obtained from carbonyl compounds and active methylene compounds [1-3], in the presence of basic catalyst or Lewis acid catalyst, such as piperidine, diethylamine, or corresponding ammonium salt [4-8]. In recent years there has been a growing interest in Knoevenagel condensation products because many of them have significant biological activity [9-13], this reaction has been widely used in organic synthesis to prepare coumarins and its derivatives, which are important intermediates in the preparation of cosmetics, perfumes, and pharmaceuticals [14,15]. Furfural and its 5-substituted derivatives were chosen as being synthetically versatile molecules with a reactive carbonyl group, they have considerable significance for their biological activities [16-19] and for their reactivity toward nucleophiles which allows the synthesis of a wide variety of heterocyclic such as nifuroxazide (NF) (condensation of 5-nitro furfural with p-hydroxy benzhydrazide) [20], which is used for the treatment of acute bacterial diarrhea [21]. In addition to that, β -dicarbonyl compounds have been studied intensively owing to their synthetic and biological significance and as well known indan-1,3-dione derivatives are important as anticoagulant drugs or rodenticides in heptate [22]. In addition to anticoagulant, Effect and rodenticidal activity, these compounds have shown parasiticidal effects, [23] analgesic, herbicidal [24].

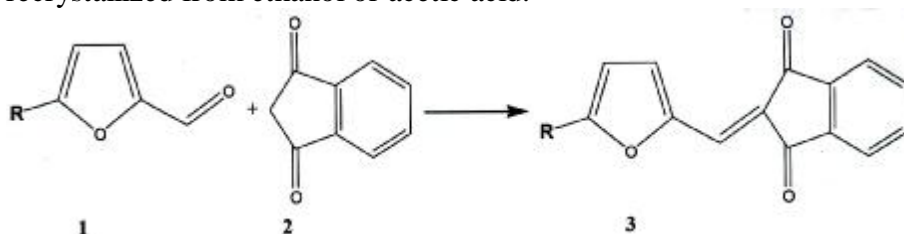
The aim of this work is the presentation of some heterocyclic derivatives of furfural as potentially useful intermediates in synthesis, and study of their structures, physical and chemical properties. As well as motivated by the aforementioned biological and pharmacological importance of the title compounds, we wish to report in future the study of expectation that the synthesized products will be of significant biological activities.

Experimental

Prepared compounds were characterized by UV spectrophotometer (Table 1), $^1\text{H-NMR}$ Spectra (Table 2) and IR spectra (Tables 3). The melting points were determined on a Kofler Block apparatus and are uncorrected. Infrared spectra were recorded in 400 - 4000 cm^{-1} region by a Specord FT-IR Jusco 300 spectrometer using KBr tablet. $^1\text{H-NMR}$ Spectra were recorded on ambient Broker DT-400 MHz spectrometer in deuterated DMSO and CDCl_3 , and UV-visible were registered with Shimadzu 190 A spectrometer (college of science – Damascus university).

Synthesis of 3a-3d

A mixture of 5-R-furfural (1a-1c) (5 mmol), Indan-1,3-dione (2) (5 mmol) in ethanol (10 ml), was stirred with simple heating until the solid was dissolved then stirred at room temperature (nearly identical yields were obtained when these reaction were performed in ethanol in the absence of catalyst at room temperature) [25], for the time given in Table(1). The solid precipitate was filtered. The products were recrystallized from ethanol or acetic acid.



Where R= a: H, b: CH_3 , c: Br, d: Cl

Results and Discussion

Four 2-(5-substitutedfurfurylidene) Indane-1,3-diones (3a-3d) were obtained by condensations of some-5-substituted furfural (1a-1d) with Indane-1,3-diones (2) in ethanol, at room temp., in normal conditions. The yields, of, prepared compounds were (46-72%).

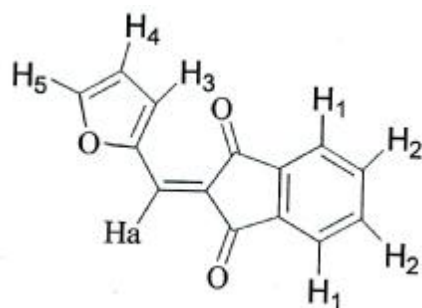
$^1\text{H-NMR}$ spectra of these compounds, indicate to disappearance of proton signals for the (methylene and proton of aldehyde groups) of the compounds (1 and 2) at δ (4,10) ppm, and appearance of a proton signal of olefine α -proton (H_α) at (6.88-7.8) ppm for all prepared compounds with the exception of 3b which appears at δ (7.68) this signal attributed to presence of methyl group [26]. Also $^1\text{H-NMR}$

spectral analysis shows proton signals of aromatic and furan ring at δ (6.4-8.6) ppm as in (Table 2). All condensation products are stable solid compounds, rather insoluble in common solvents, with high melting points. (Table 1). The resonance signals and their multiplicity confirmed the proposed structures. The infrared spectra of the prepared compounds (3a-3d) showed strong absorption bands of the C=C, and C=O stretching vibrations in two very well distinguished regions (1620– 1680) cm^{-1} and (1695 – 1750) cm^{-1} . The C=O stretching frequencies for carbon-carbon double bond conjugated systems are generally lower by 25-45 cm^{-1} than those of corresponding non-conjugated compounds. The delocalization of π -electrons in the C=O and C=C bonds lead to partial double bond character in C=O and C=C bonds and lowers the force constant, and The presence of two conjugated groups as in benzophenone further lowers the C=O stretching frequency [27], this means that founding of withdrawing group will decrease stretching frequencies of carbonyl group, as it found in previous study [28]. (Table 3). The absorption bands in the lower region of the spectra (1400-1600) cm^{-1} belong to the (C=C) of the furan ring, Ar-ring. The compounds 3c,3d showed the (C=C) band at 1625-1627) cm^{-1} . Strong band due to the presence of withdrawing group and its conjugation effect with furan ring (Table 3).UV spectra showed red-shift phenomena for all prepared compounds attributed to furan ring as the conjugated with formed C=C bond conjugation of the carbonyl group with double bond shifts both $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions to longer wavelengths [27], compound 3b show simple lowerest in λ_{max} du to presence of doner group table (1). Where λ_{max} for furfural is (329nm) while λ_{max} for indan is (358nm).

Table 1.Characterization of the prepared compounds

Comps.	R	Product s names	Moleculer Formula	m.p. °C	Yield %	Tr min or (hr)	λ_{max} . nm
3a*	H	2-(furfurylidene) Indane-1,3-dione	$\text{C}_{14}\text{H}_8\text{O}_3$ 224.21	203-205	50	2.5hr	366,390
3b	CH_3	2-(5-methyl-furfurylidene) Indane-1,3-dione	$\text{C}_{15}\text{H}_{10}\text{O}_3$ 238.24	188-189	51	3.5hr	372,385
3c	Br	2-(5-bromo-furfurylidene) Indane-1,3-dione	$\text{C}_{14}\text{H}_7\text{BrO}_3$ 303.11	193-195	68	1.5hr	396,405
3d	Cl	2-(5-chloro-furfurylidene) Indane-1,3-dione	$\text{C}_{14}\text{H}_7\text{ClO}_3$ 258.66	191-193	46	2.5hr	395,398

*=this compound was published in another journal but written here just for comparison.

Table 2. ¹H NMR spectra data of prepared compounds.

COMP.	SOLVENT	¹ H NMR spectrum (ppm)	Fig.
3a	CDCl ₃	δ: 7.78 (s, 1H, Ha); 7.78, 7.79-7.82, 8.61 (7H, 4H-ArH, 3H-furan ring).	1
3b	CDCl ₃	δ: 2.49 (s, 3H-CH ₃); 6.88 (s, 1H, Ha); 6.41, 7.77-7.78, 7.97-7.98, 8.5 (6H, 4H-arom. and 2H-furanes)	2
3c	CDCl ₃	δ: 7.72 (s, 1H, Ha); 6.92, 7.79-7.82, 7.97-8.00, 8.46 (6H, 4H-arom. and 2H furanes).	3
3d	CDCl ₃	δ: 7.7 (s, 1H, c=Ha); 7.4, 7.88-7.73, 8.05-8.08, 8.64 (6, 4H-arom. and 2H-furanes).	

Table 3. IR spectral data of synthesized compounds 3a-d.

Comp.	$\bar{\nu}$ C=O	$\bar{\nu}$ C=C furan, Ar	$\bar{\nu}$ C=C
3a	1745, 1695	1412, 1570	1680
3b	1758, 1700	1413-1562, 1590	1653
3c	1720, 1690	1425, 1540, 1580	1627
3d	1730, 1690	1400, 1470, 1590	1625

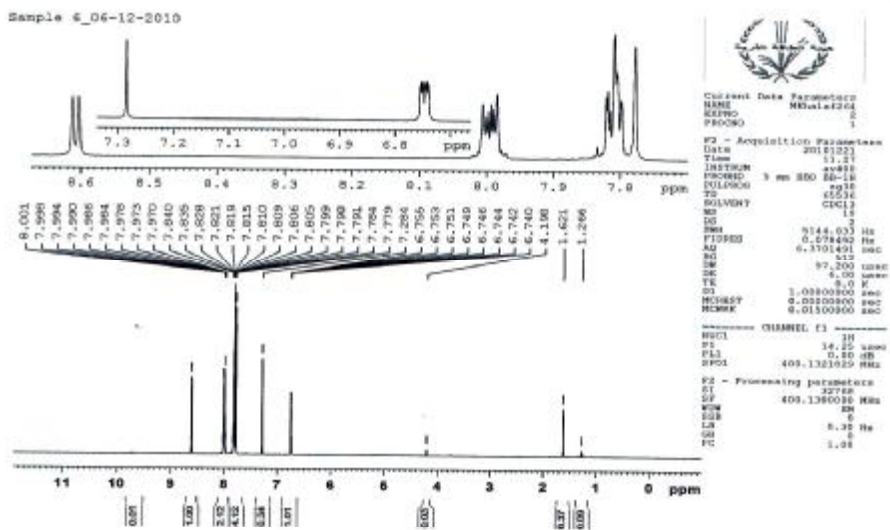


FIG.1: ¹H NMR spectrum of comp.3a

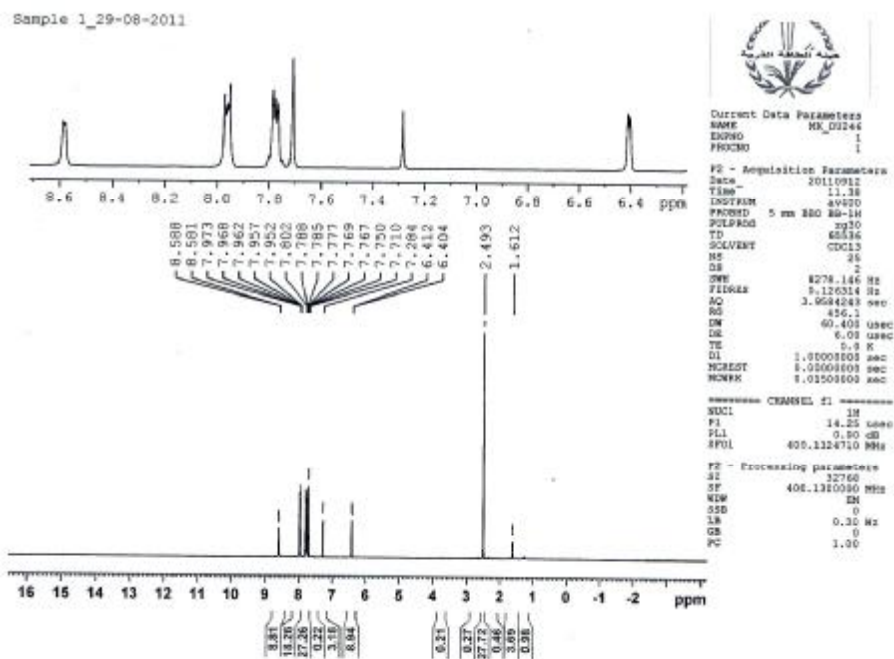


FIG.2: ¹H NMR spectrum of comp.3b

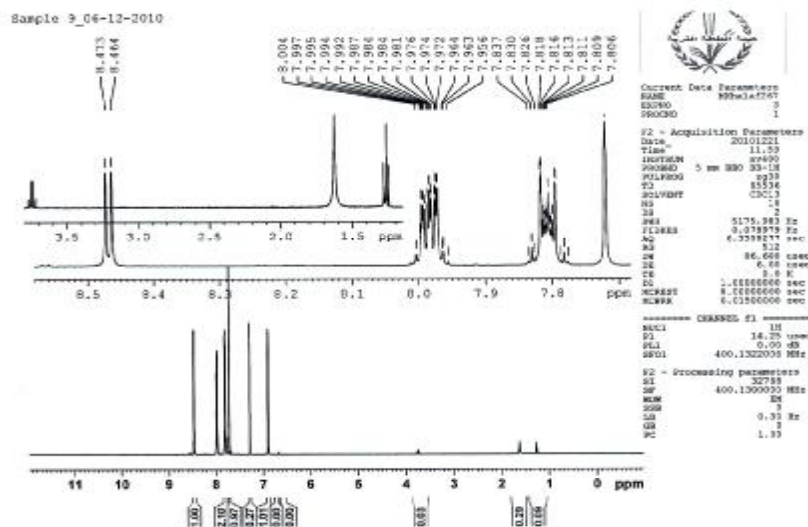


FIG.3: ¹H NMR spectrum of comp.3c

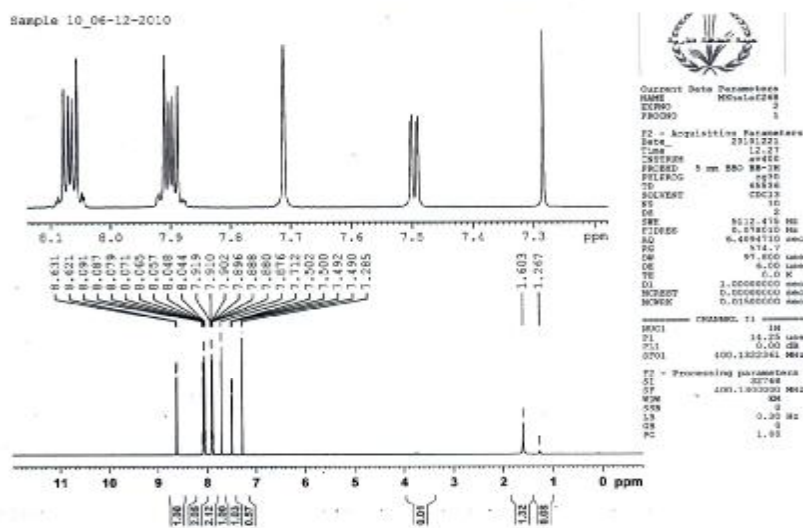


FIG.4: ¹H NMR spectrum of comp.3d

Note: all figures show signal at δ: 1.6 ppm attributed to solvent with moistures

Conclusions

The reaction at room temperature with absence of catalyst will give ideal product as well as it will provide a simple and inexpensive experiment to get the compounds.

REFERENCES

- 1-Sebti S., Rhihil A., Saber A. (1995). ChemInform Abstract: Natural Phosphate and Sodium Phosphate: Novel Solid Catalysts for Knoevenagel Condensation in Heterogeneous Medium. *ChemInform*,26(19),9
- 2-(a)Sebti S., Rhihil A., Saber A.,Hanafi N., (1996). Natural phosphate doped with potassium fluoride and modified with sodium nitrate: efficient catalysts for the Knoevenagel condensation. *tetrahedron letters*, (37), 6555; (b) Sebti S., Rhihil A.,Saber A., Laghrissi M., Boulaajaj S. (1996). efficient catalysts for the Knoevenagel condensation. *tetrahedron letters*, (37), 3999,;(c) Sebti S., Boukhal H., Hanafi N Boulaajaj S. (1999)-*tetrahedron letterst*,(40),6207.
- 3-Anastas P., Warner J. (1998). Green Chemistry: Theory and Practice. Oxford University Press: Oxford.
- 4-Raop S., Venkataratnam R. (1991). Zinc Chloride as a New Catalyst for Knoevenagel Condensation. *Tetrahedron Letters*, (32), 5821.
- 5-Delacruz P., Diezbarra E., Loupy A., Langa F. (1996). "Silica gel catalysedKnoevenagel condensation in dry media under microwave irradiation". *Tetrahedron Letters*,(37), 107-111.
- 6- Balalaie S., Nemati N. (2000). Ammonium acetate-basic alumina catalyzed Knoevenagel condensation under microwave irradiation under solvent-free conditions. *Synthetic.Communication.*(30), 869.
- 7- Bigi F., Conforti M., Maggi R., Piccinno A., Sartori G. (2000). Clean synthesis in water: Uncatalysed preparation of ylidenemalononitriles. *Green Chemistry* (2), 101-103.
- 8- Dalko P., Moisin L. (2004). Laboratoire de Recherches Organiques associé au. *Angew.Chemistry.International. Education*,(43), 5138.
- 9- Tietze L., Rackelman N., Zhu J., Bienayme H. (2005). The Domino-Knoevenagel-hetero-Diels-Alder Reaction In Multicomponent Reactions. *Educatons,Wiley-VCH, Weinheim*, 121.
- 10- (A) Cui H., Li P., Chai Z., Zheng C., Zhao G., Zhu S. (2009). Laboratory of Modern Synthetic Organic Chemistry. *Journal of organic chemistry.* (74), 1400. (b) HU M., LI J.,YAO S Q.,(2008)- In Situ "Click" Assembly of Small Molecule Matrix Metalloprotease Inhibitors Containing Zinc-Chelating Groups. . *Organic. Letters.* (10), 5529.
- 11- Qin P., Zhu H., Edvisson T., Boschloo, G., Hagfeldt, A., Sun L. (2008). Design of an organic chromophore for p-type dye-sensitized solar cells. *Journal of.American Chemical S occity*,(130), 8570.
- 12-Zhang X., Chao W., Chuai Y.,Ma Y., Hao R., Zou D., Wei Y., Wang Y. (2006). A new N-type organic semiconductor synthesized by knoevenagelcondensation of truxenone and ethyl cyanoacetate. *Organic. Letters*, (8), 2563.
- 13-(a) Kwak V., Fujiki M. (2004). Synthesis of polyelectrolyte gels with embedded voids having charged walls. *Macromolecules*, (37), 2021. (b) Liao J., Wang Q. (2004). Synthesis of Telechelic Fluoropolymers... Poly(p-phenylenevinylene)s,"*Macromolecules* (37), 7061. (c) Nokami J.,Kataka K., Shiraishi K., Osafune M., Hussain I., Sumida S., 2001- *Journal of Organic. Chemistry*, (66), 1228.

- 14-(a) Jones G. (1967). Knoevenagel Condensation; Doebner Modification. *Organic reaction*, (15), 204. (b) Bose D., Narsaiah A. (2001). Cadmium chloride-catalyzed regioselective opening of oxiranes with aromatic amines--an improved protocol for the synthesis of 2-amino alcohols, *Journal of Chemical Res.(S)*(1)36.
- 15- Bigi F., Chesini L., Maggi R. and Sartory G. (1999). Highly efficient synthesis of coumarin derivatives in the presence of $H_{14}[NaP_5W_{30}O_{110}]$ as a green and reusable catalyst *Journal of Organic. Chemistry*, 64
- 16-Rabarova E., Kois P., Lacova M., Krutosikova A. (2004). Microwave assisted synthesis of substituted furan-2-carboxaldehydes and their reactions, *ARKIVOK*, (i), 110–122.
- 17- Lacova M., Gasparova R., Loos D., And Pronayovov T. (2000). Effect of Microwave Irradiation on the Condensation of 6-Substituted 3-Formylchromones with Some Five-membered Heterocyclic Compounds. *Molecules*, (5), 167.
- 18- Akira T., Nan Y., Cheinh H. (1970). Reactions of substituted furo[3,2-b]pyrrole-5-carboxhydrazides and their biological activity Shigetaka. *YakugakuZasshi* (90), 1150, (CA, 73: 120433x (1970)).
- 19-Shindhar D. R., Sastry C. V., Vadya N. K. (1981). Synthesis and Antimicrobial... furaldehydes and 3-(5-Nitro-2-furyl)acrolein.. *J. Indian Chem. Soc.* 57, 1118 (CA, 94: 174765j (1981)).
- 20-El Obeid, H. A., Elnima, E. L., Al-Badr, A. A. (1985). Synthesis and Antimicrobial Activity of New Furan Derivatives. *Pharm. Res.* (42).
- 21-Tabacovic R., and Tabacovic I. (1999). Catalysis of nifuroxazide formation by crosslinked poly (vinylpyridinesupported acids). *Reactive Funct. Poly*, (39), 263–268.
- 22-William W. Ogilvie, A, YNathalie Goudreau, A Julie Naud, A Bruno Hache, A Jeff A. O'Meara, a Michael G. (2003). Discovery of the First Series of Inhibitors of Human Papillomavirus Type 11: Inhibition of the Assembly of the E1–E2–Origin DNA Complex.. *Bioorganic & Medicinal Chemistry Letters* 13, 2539–2541.
- 23-Hideomi Takahashia, JochenSchmalfu. A, Aiko Ohkia, Akemi Hosokawab, Akira Tanakac, Yukihar Satoa Bernd Matthesd, Peter B.ger*,d and Ko Wakabayashi.. (2002). nhibition of Very-Long-Chain Fatty Acid Formation by Indanofan, 2-[2-(3-Chlorophenyl) oxiran-2-ylmethyl]-2-ethylindan-1,3-dione, and Its Relatives. *Z. Naturforsch.* 57c, 72D74
- 24-Akemi Hosokawa, Toyohiko shike, Manabu Katsurada, Osamu ikeda, Noriko minami and Tetsuo jikihara.. (2001). Synthesis and Herbicidal Activity of Indanofan and Related 2-(2-Phenylloxiran-2-ylmethyl) indan-1,3-dione Derivatives. *J. Pestic. Sci.* 26, 41-47
- 25-Subodh Kumar. (2006). Spectroscopy of Organic Compounds Guru Nanak Dev University, Amritsar, book, p29-32.
- 26-Franz, C.; Heinisch G.; Holzer W.; Mereiter K.; Strobe B.; Zheng C. (1995). Reaction products of... structure and NMR-investigations. *Heterocycles*, 41, 2527.
- 27-Hassan M., Al-Alazimi A., Monirah Al-Shaikh, (2010). Microwave assisted synthesis of substituted furan-2-carboxaldehydes and their reaction, *journal of Saudi Chemical Society*, 14, p379.
- 28-Kolnevetsh F. G, Grabevin D.G., Abdulwahab A. (1993). Synthesis and characterization of thiohydantoin and thiobarbituric furan derivatives, thesis, p28.