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Mendeleev Commun., 2019, **29**, 174–175

Mendeleev Communications

2,3,5-Trichlorocyclopent-2-enone derivatives in the Friedel–Crafts reaction with methoxybenzenes and the anticancer activity of the products

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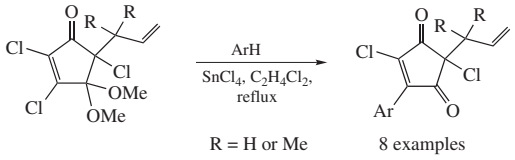
DOI: 10.1016/j.mencom.2019.03.019

The Friedel–Crafts-type reaction of 5-allyl-2,3,5-trichlorocyclopent-2-enones with mono-, di- and trimethoxybenzenes affords the arene ketovinylation products with the cleavage of C^3–Cl bond in the starting trichlorocyclopentenones. The cytotoxicity of the products toward normal HEK293 cell lines and three cancer cell lines, SH-SY5Y, A549 and MCF-7, was evaluated.



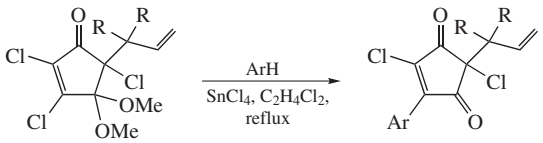
The alkylation/acylation of aromatic and heteroaromatic compounds, olefins and acetylenes with alkyl/acyl halides or anhydrides catalyzed by Lewis or Brønsted acids, recognized as the Friedel–Crafts reaction (FCR), is among the fundamental methods in organic synthesis.[1–5]

Previously, we reported reactions of selective C^3-substitution in trichlorocyclopentenones **1** and relative 2,3-dichloro-1*H*-inden-1-ones with N-, O-, S- and C-nucleophiles.[6–9] These reactions smoothly occurred *via* the Ad$_N$E-replacement of the vinylic Cl atom at C^3 to give corresponding substitution products in good yields. The close precedents are the regioselective Suzuki–Miyaura arylation and Sonagashira alkynylation of 2,3-dibromo-1*H*-inden-1-one.[10] 2,3,5-Tribromoinden-1-one underwent site-selective Suzuki–Miyaura 1,3-diarylation with arylboronic acids.[10(*c*)]

Considering the structures of trichlorocyclopentenones **1** as a vinylogue of acid chlorides, in this study we tested them as electrophiles in the FCR with arenes. The high reactivity of the C^3–Cl bond in trichlorocyclopentenone **1** (Scheme 1) allowed us to expect that intermediate ion-pair complexes **A** responsible for the subsequent steps of acylation of aromatic compounds can be generated with participation of Lewis acids. Alternatively, the possibility of the reaction pathway *via* enol-type intermediate **B** (the Nazarov's cation) cannot be ruled out.

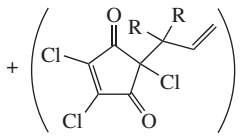
In a preliminary experiment under typical FCR conditions (CH_2Cl_2, ~20 °C), trichlorocyclopentenone **1a**[7] did not react with phloroglucinol trimethyl ether in the presence of $ZnCl_2$, $AlCl_3$ or $SnCl_4$ as a catalyst. Meantime, this reaction successfully occurred under more drastic conditions in refluxed dichloroethane containing $SnCl_4$ to afford the ketovinylation product **2a** in 85% yield (Scheme 2).† Under the same conditions, the *gem*-dimethyl-containing trichlorocyclopentenone **1b**[11] gave the ketovinylation product **3a** in a lower yield (58%).

Trichlorocyclopentenones **1a** and **1b** reacted with other (poly)-methoxybenzenes in a similar way to furnish the expected products **2b–d** and **3b**,**c**, respectively. In cases of 1,2,3-trimethoxy-, 1,4-dimethoxybenzenes and anisole, small amounts (5–10%) of



1a R = H
1b R = Me

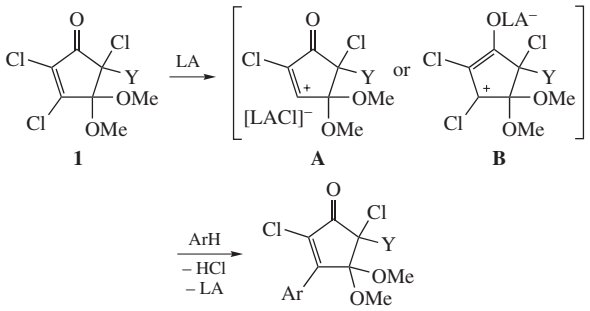
2a–e, **3a–c**



4 R = H (8% with **2b**, 40% with **2e**)
5 R = Me (10% with **3b**, 5% with **3c**)

	R	Ar	Yield (%)
2a	H	2,4,6-(MeO)$_3$C$_6$H$_2$	85
2b	H	2,3,4-(MeO)$_3$C$_6$H$_2$	54
2c	H	2,5-(MeO)$_2$C$_6$H$_3$	84
2d	H	4-MeOC$_6$H$_4$	60
2e	H	2-HO-4-ClC$_6$H$_3$	26
3a	Me	2,4,6-(MeO)$_3$C$_6$H$_2$	58
3b	Me	2,3,4-(MeO)$_3$C$_6$H$_2$	51
3c	Me	2,5-(MeO)$_2$C$_6$H$_3$	68

Scheme 2



1 **A** **B**

Scheme 1 LA is a Lewis acid.

† *2-Allyl-2,4-dichloro-5-(2,4,6-trimethoxyphenyl)cyclopent-4-ene-1,3-dione* **2a**. 1,3,5-Trimethoxybenzene (75.6 mg, 0.35 mmol) and $SnCl_4$ (0.08 ml) were added to a stirred solution of trichlorocyclopentenone **1a** (0.1 g, 0.35 mmol) in dichloroethane (20 ml) and the reaction mixture was refluxed for 5 h (TLC). The reaction mass was then cooled to room temperature, distilled water (15 ml) was added, and the mixture was diluted with $CHCl_3$ (15 ml). The organic layer was separated, washed with a saturated $NaHCO_3$ solution (2×15 ml) and dried over $MgSO_4$. The solvent was evaporated, and the residue was purified by column chromatography on silica gel (EtOAc–light petroleum, 1 : 10). Yield 0.11 g (85%). Bright yellow crystals, mp 115–116 °C. IR (ν/cm^{-1}): 1723, 1610, 1584, 1472, 1457, 1419, 1287, 1229, 1207, 1165, 1152, 1131. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.90 (dd, 2 H, CH_2, *J* 3.7 and 7.3 Hz,), 3.74 (s, 3 H, OMe), 3.77 (s, 3 H, OMe), 3.84 (s, 3 H, OMe), 5.17 (dd, 2 H, =CH_2, *J* 17.1 and 9.9 Hz),

diones **4**[12] and **5**, *i.e.*, the products of the dimethylacetal protective group hydrolysis, were formed. The FCR of compound **1a** with *m*-chlorophenol provided a lower yield (26%) of product **2e**, while cyclopentenedione **4** was the major one.

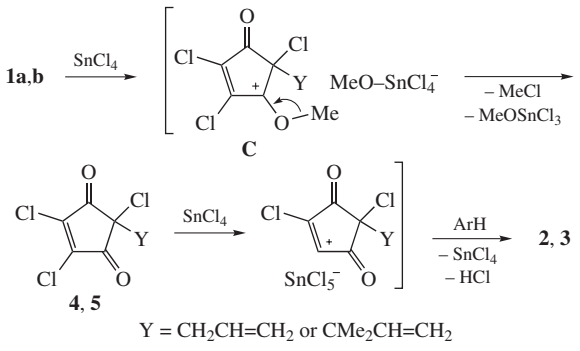
Based on the structures of starting trichlorocyclopentenones **1a**,**b** and products **2**, **3**, one can conclude that the process involves deblocking of the dimethylketal function at C^4 atom. This can be explained by the generation of methoxycarbenium intermediates **C** under the action of $SnCl_4$ (Scheme 3). These species are transformed into cyclopentenediones **4**, **5** which are more reactive in C^3–Cl substitution reactions. Diones **4**, **5** were isolated as minor products in some of the experiments (see Scheme 2)

Note that compounds **1a**,**b** and similar 2,3-dichlorocyclopentenones and acrylates[13] were not involved in the FCR. A precedent resembling the reactions under discussion was observed in the acylation of arenes with squaric acid dichloride in the $AlCl_3$–$CHCl_3$ system.[14] Furthermore, we found several examples of Friedel–Crafts intramolecular cyclizations of β-chlorovinyl ketones generated *in situ*.[15]

The structures of compounds herein prepared relate to Piperlongumine amide-type alkaloid[16] and Typosine Kinase Inhibitor TX-1123,[17] which show cytotoxicity toward a wide range of cancer cells, and a natural compound coruscanone with antifungal action.[18] It is of note that the presence of important pharmacophore signatures, *viz.*, an aryl substituent, methylidenecyclopentenedione and β-arylacrylamide, is typical of the compounds in question.

Obviously, the starting compounds **1a**,**b** and the ketovinylation products **2**, **3** are synthetically attractive objects. Various heterocyclizations, conversion of the allylic side chain to an acrylate one, reactions involving Cl atoms and carbonyls as well as new cyclopentenedione chemistry may be expected for these compounds.[6] In addition, products **2**, **3** seem interesting as new bioactive substances and precursors for further conversion to more complex compounds.

The cytotoxic activity of compounds **2a**,**c** and **3a**,**c** was studied by MTT test in conditionally normal HEK293 cells and three cancer cell lines (A549, MCF-7, SH-SY5Y). The results are summarized in Table 1 as the concentration of a compound providing 50% inhibition of cell metabolic activity (IC_{50}). The tested compounds exhibit moderate cytotoxic effect in all cell lines with prominent activity predominantly towards SH-SY5Y neuroblastoma cells (with IC_{50} values of < 10 μM for substances **2a**,**c**, **3c**), whilst lung carcinoma A549 cell line proves less sensitive to the action of all of the studied compounds.



Scheme 3

Table 1 IC_{50} values of compounds **2a**,**c** and **3a**,**c** against HEK293, SH-SY5Y, A549 and MCF-7 cell lines.[a]

Compound	DMSO	IC_{50}/μM			
		HEK293	SH-SY5Y	A549	MCF-7
2a	+	15.54 ± 1.05	3.25 ± 0.40	22.84 ± 0.54	1.47 ± 0.15
2c	+	28.35 ± 11.87	19.46 ± 3.40	68.37 ± 2.84	47.56 ± 4.46
3a	+	11.47 ± 3.40	17.73 ± 0.01	46.60 ± 3.13 ($p = 6\times10^{-6}$)[b]	16.35 ± 3.27
3c	+	12.47 ± 3.96	7.50 ± 1.53	33.93 ± 9.67	16.31 ± 0.50

[a] Cells were incubated with compounds for 48 h. Data are given as mean values ± SEM of two independent experiments performed in triplicate. [b] *p*-Values indicate comparisons of A549, MCF-7 and SH-SY5Y with HEK293 cells using one-way ANOVA with Dunnett's post-hoc test.

This study was carried out within the framework of the State task (project no. AAAA-A17-117011910032-4). The spectral and analytical studies were performed using the equipment of the Khimiya Joint Center, Ufa Institute of Chemistry, Russian Academy of Sciences.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.03.019.

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Received: 5th September 2018; Com. 18/5681

5.62 (ddd, 1H, =CH, *J* 7.3, 10.0 and 17.3 Hz,), 6.16 (s, 1H, H_{Ar}), 6.17 (s, 1H, H_{Ar}). ^{13}H NMR (125 MHz, $CDCl_3$) δ: 39.8 (CH_2), 55.5 (OMe), 55.8 (OMe), 61.7 (C^2), 90.8 (C^3_{Ar}), 90.9 (C^5_{Ar}), 97.6 (C^1_{Ar}), 121.7 (=CH_2), 128.9 (=CH), 151.1 (C^5), 151.9 (C^4), 158.9, 159.2, 164.5 (C^2_{Ar}, C^4_{Ar}, C^6_{Ar}), 189.9 (C=O), 191.6 (C=O). MS (EI), *m*/*z* (%): 371 (372, 373) $[MH]^+$ (100), 355 (356, 357) $[M-Me]^+$ (45). Found (%): C, 55.35; H, 4.21; Cl, 19.48. Calc. for $C_{17}H_{16}Cl_2O_5$ (%): C, 55.00; H, 4.34; Cl, 19.10.

For characteristics of compounds **2b**–**e**, **3a**–**c**, **4** and **5**, see Online Supplementary Materials.