Combinatorial Knoevenagel Reactions

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Chlorotrimethylsilane (TMSCl) has been utilized as an efficient promoter and water scavenger in the Knoevenagel condensations of aromatic aldehydes with various methylene active compounds. High yields and a simple workup of target compounds enables the facile generation of combinatorial libraries comprising 11 000 compounds of high structural and functional diversity.

Introduction

The Knoevenagel reaction is a facile and versatile method for the formation of carbon–carbon bonds.[1,2] It has been widely used to synthesize coumarins and their derivatives, which are important intermediates in the cosmetic and pharmaceutical industries.[2] Various products of the Knoevenagel reactions have been proved to be efficient enzyme inhibitors as well as antitumor, anti-inflammatory, and antibacterial agents.[3] Thus, it is apparent that the elaboration of a simple and facile synthetic procedure for the Knoevenagel reactions is an important scientific and practical challenge.

The homogeneous Knoevenagel reactions are normally carried out in the presence of weak bases such as ethylenediamine, piperidine, potassium fluoride, and amino acids,[1,2,4] whereas the acid-catalyzed reactions are relatively scarce.[1,2] Recently, considerable research attention has been focused upon the heterogeneous Knoevenagel condensations promoted by aluminium oxide, MgO, titanium tetrachloride, Xonotlite/tert-butoxide, cation-exchanged zeolites, alkali-containing MCM-41, SiO_2, calcite, fluorite, modified Mg-Al hydrotalcite, and Lewis acidic ionic liquids.[5–9] Thorough analysis of the literature data indicated that none of the described procedures can be used to generate large sets of compounds for high-throughput biological screening because of low conversion and complicated purification protocols.

In our search for a facile preparative procedure for the solution-phase combinatorial Knoevenagel reaction, we considered Me_3SiCl as a promising promoter and water scavenger[10] since it has been successfully used in several other condensation reactions. Herein, we report an optimized synthetic procedure for the combinatorial Knoevenagel reactions which furnished 11 000 target compounds in the course of 13 000 parallel syntheses.

Results and Discussion

It has been found previously that the reactivity of aromatic aldehydes in Me_3SiCl-promoted[10,11] condensation reactions is virtually independent on the nature of the substituents in the aromatic ring.[10b,c] To optimize the reaction conditions, we carried out a model series of the Knoevenagel reactions of benzaldehyde **1(1)**, 4-methoxybenzaldehyde **1(2)**, and 4-chlorobenzaldehyde **1(3)**.

The Knoevenagel reactions of these aldehydes with malonodinitrile **2(1)** and ethyl cyanoacetate **2(2)** in *N*,*N*-dimethylformamide (DMF) in the presence of three molar equivalents of Me_3SiCl at 100 °C (sealed tube) gave compounds **3**{**1(2)**–**2(1)**} and **3**{**1(2)**–**2(2)**}, which after precipitation with water and washing with methanol were isolated in >95% purity (according to liquid chromatography–mass spectrometry, LCMS) and nearly quantitative preparative yields. This optimal set of conditions was applied to the reactions of other methylene active compounds.

Amides **2(3–9)** react with aldehydes similarly to compounds **2(1,2)**, and the nature of the amido group does not affect the yields of the products. The Knoevenagel reaction of tertiary amide **2(10)** occurs partially, to give after chromatography the target compounds in somewhat lower yields. On the other hand, the substitution of one nitrile group of malonodinitrile by carbonyl, sulfonyl, or hetaryl groups (compounds **2(11–13)**, **2(14,15)**, and **4(1–12)**, respectively) virtually does not affect the yields of target compounds (Scheme 1).

Surprisingly, phenylacetonitrile **4(13)** does not react with aldehydes under the optimized conditions, most probably due to its relatively low CH acidity. More CH-acidic *p*-nitrophenylacetonitrile **4(14)** underwent the Knoevenagel reactions with aldehydes upon 8 hrs of heating at 100 °C. However, the incomplete conversion (<75%) required chromatographic purification of the products. Under more drastic conditions, such as higher temperatures or longer

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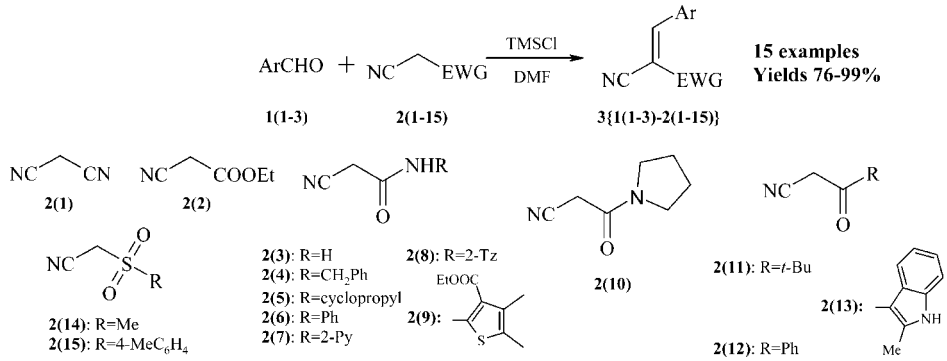
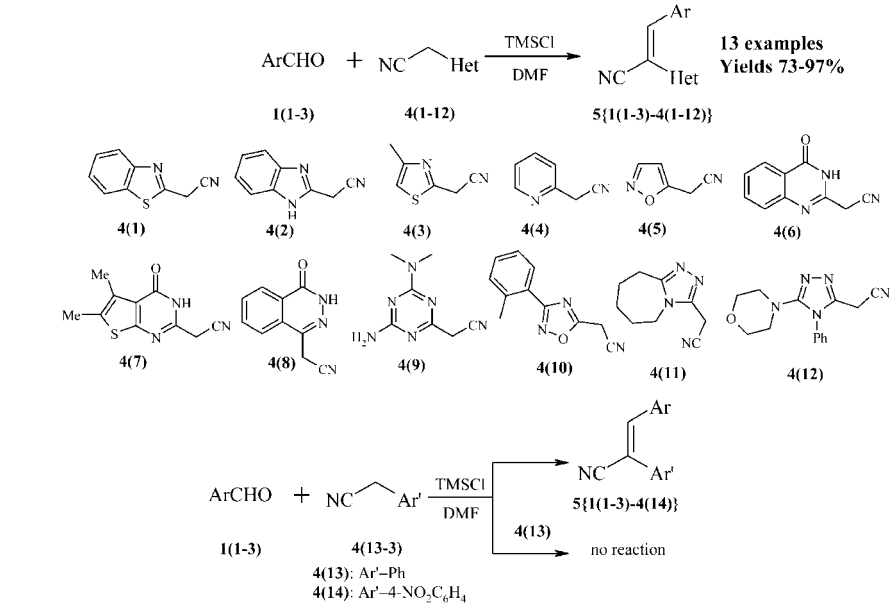
Scheme 1



Scheme 2

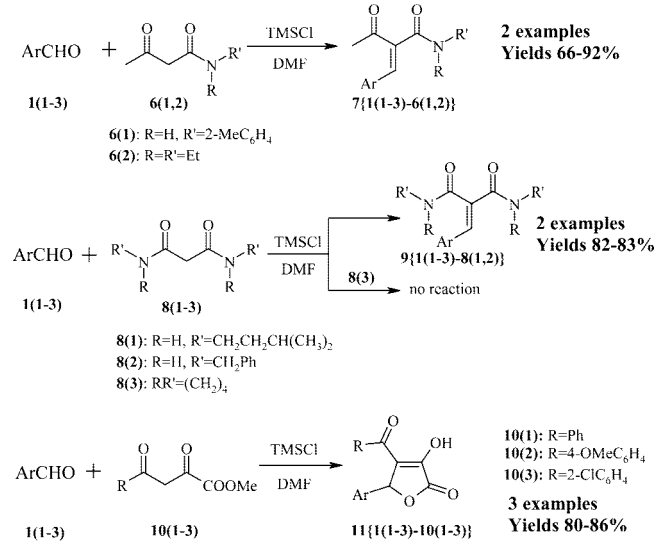


reaction times, the yields of target compounds did not increase, but side reactions led to unidentified byproducts (Scheme 2).

Acetoacetamides **6(1–2)** appeared to be unstable at 100 °C; however, they reacted with carbonyl compounds at ambient temperatures to give products **7** in preparative yields. The dependence of conversion on the type of amide groups was identical to that observed for the cyanoacetamides (see above). The Knoevenagel reaction of malonodiamides **8(1,2)** carried out for 8–10 h at 100 °C led to products **9**{**1(1–3)**–**8(1,2)**} in high yields, whereas compound **8(3)** did not react at this temperature (reaction time 8–24 h; Scheme 3). The different reactivity of the primary, secondary, and tertiary methylene active amides can be associated with decreasing the CH acidity caused by positive inductive effects of the aliphatic substituents and probably some steric strain. The reaction of aldehydes **1** with benzoylpyruvates **10(1–3)** resulted in heterocyclization to give hydroxypyranons **11**{**1(1–3)**–**10(1–3)**}.[12]

Various cyclic methylene active compounds readily underwent the TMSCl-promoted Knoevenagel reactions with aldehydes **1(1–3)**. For example, the reactions of compounds **12(1–9)** at 100 °C gave mixtures of 1:1 and 2:1 condensation products **13** and **14** (Scheme 4), whereas at 25 °C, only the benzylidene compounds were obtained in high preparative

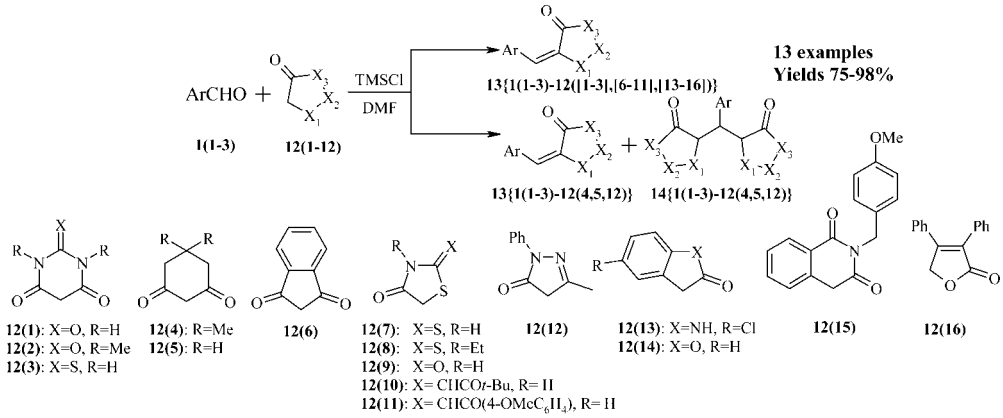
Scheme 3



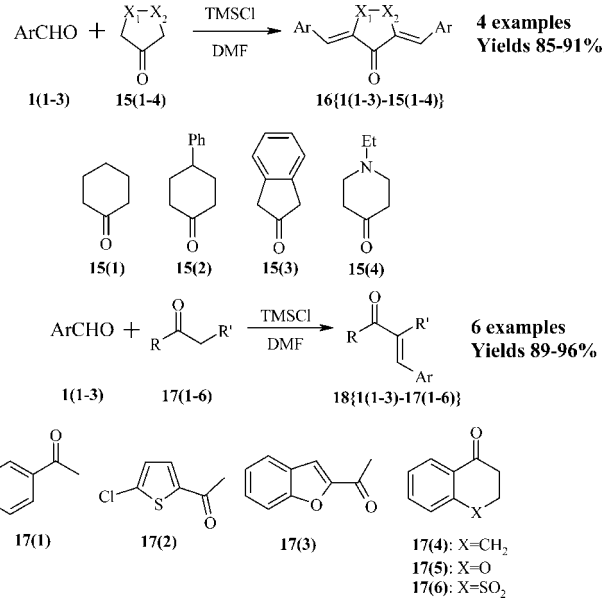
yields. On the other hand, the less CH-acidic compounds **12(13–16)** gave benzylidene derivatives **13**{**1(1–3)**–**12(13–16)**} at 25 and 100 °C.

The TMSCl-promoted Knoevenagel reactions of cyclic and acyclic ketones possessing active methylene and methyl

Scheme 4



Scheme 5

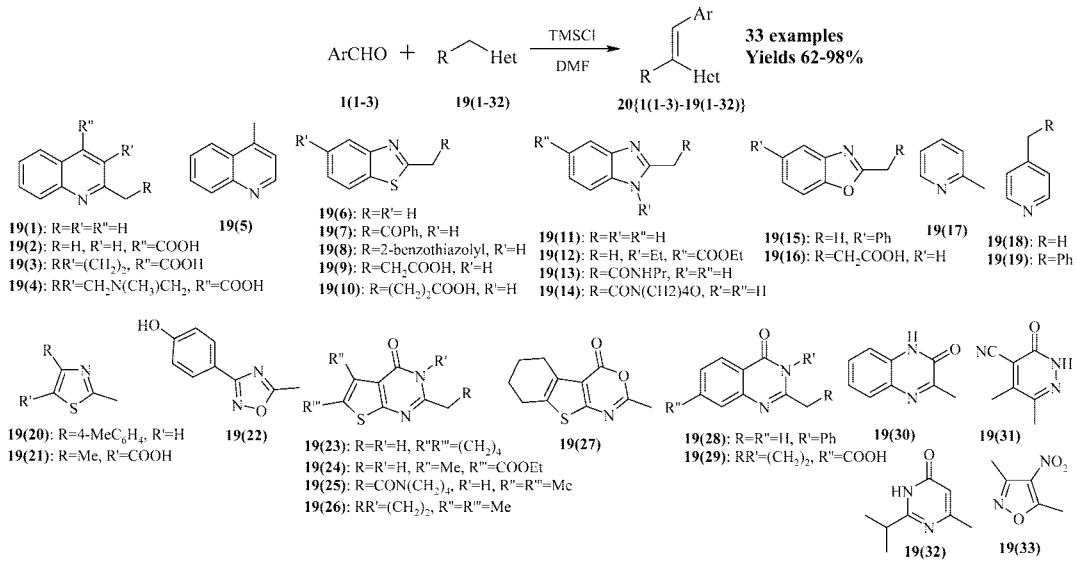


groups led to benzylidenes and bis-benzylidenes in high yields and with excellent purity (Scheme 5).

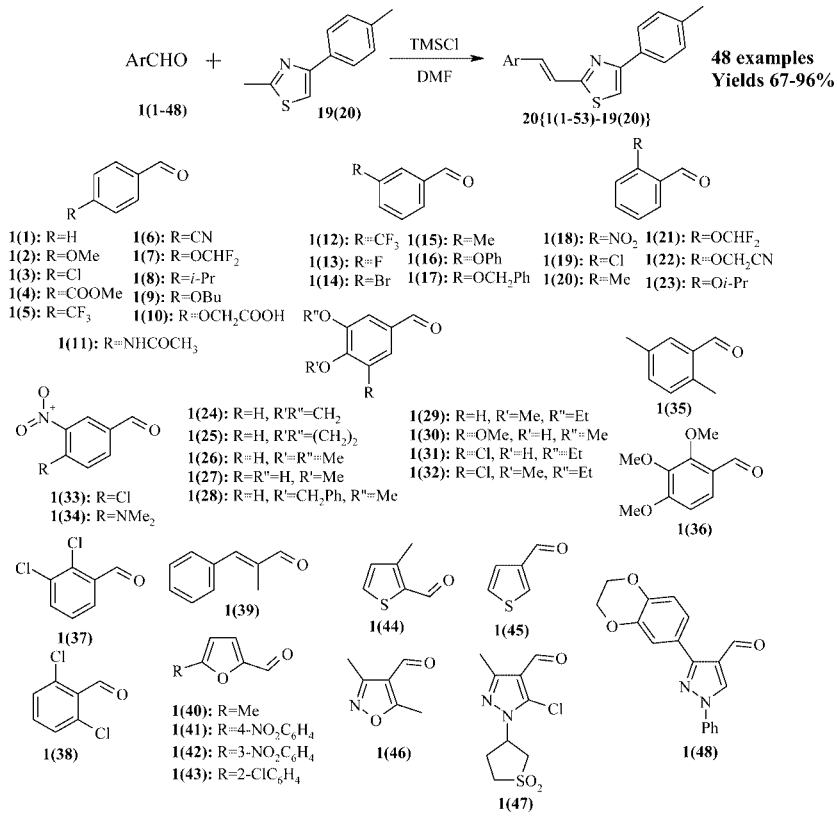
The Knoevenagel reactions of heterocycles bearing CH-acidic methyl and methylene groups and carbonyl compounds gave styryles, some of which exhibited a wide spectrum of physiological activities.[13] However the known synthetic protocols for such reactions employ strong bases (NaH, NaOAlk, and NaOH),[14] Lewis acids ($ZnCl_2$ and BF_3),[15] and Ac_2O at high temperatures (140–220 °C)[16] or microwave assistance.[17] The harshness of these conditions impedes their use in the combinatorial synthesis of styryls.

The Knoevenagel reactions of quinolines **19(1–5)**, benzothiazoles **19(6–10)**, benzimidazoles **19(11–14)**, benzoxazoles **19(15,16)**, pyridines **19(17–19)**, thiazoles **19(20,21)**, 1,2,4-oxadiazole **19(22)**, thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **19(23–26)**, and 4*H*-thieno[2,3-*d*][1,3]oxazin-4-one **19(27)** with aldehydes **1(1–3)** carried out for 8–24 h in DMF in the presence of TMSCl at 100 °C led to the corresponding styryls **20** in high preparative yields. Simple precipitation of compounds **20** with water and washing with methanol assures their >90% purity. The presence of an –M substituent in the heterocyclic rings of compounds **19(2–4,12,15)** increases their activity so that the conversion to the corresponding compounds **20** requires shorter reaction time. Apparently, this is caused by the increase of CH acidity of the methyl group. Even more reactive are compounds **19(7,8,13,14)** whose CH acidity are increased by the –I effect of the amide residues directly bound to the methylene groups. The

Scheme 6



Scheme 7



Knoevenagel reactions occur at ambient temperature (reaction time 12–24 h) to give the corresponding styryls in almost quantitative yields.

Quinazolin-4(3*H*)-ones **19(28,29)**, 3-methylquinoxalin-2(1*H*)-one **19(30)**, 5,6-dimethyl-3-oxo-2,3-dihydropyridazine-4-carbonitrile **19(31)**, 2-isopropyl-6-methylpyrimidin-4(3*H*)-one **19(32)**, and 3,5-dimethyl-4-nitroisoxazole **19(33)** appeared to be less reactive than compounds **19(1–27)** since their Knoevenagel reactions (DMF, TMSCl, 100 °C) required much longer reaction times (20–25 h), to give the corresponding styryls in nearly quantitative yields (Scheme 6).

In order to ascertain the scope and limitation of the TMSCl-promoted Knoevenagel condensation, the least reactive 2-methyl-(4-tolyl)thiazole **19(20)** was reacted with 48 arylaldehydes **1(1–48)** to give a library of styryls {**20(1–48)**–**19(20)**} (Scheme 7).

The composition and structure of all the compounds obtained was proved by mass spectrometry, elemental analysis, and NMR spectroscopy. The configurations of the double bonds were established on the basis of 1D nuclear Overhauser effect spectrometry (NOESY) NMR studies and the values of coupling constants in ^{1}H NMR spectra (Figure 1a). The ^{1}H–^{13}C heteronuclear multiple-bond correlation (HMBC) cross-peaks (Figure 1b) unambiguously prove that the *para*-chlorobenzylidene group in compound **20**{**1(3)**–**19(31)**} is situated in the ortho position to the nitrile fragment. The correlations for compound **20**{**1(2)**–**19(33)**} clearly indicate that the *para*-methoxybenzylidene fragment is bonded to the 5 position of the oxazole ring.

It seems plausible that TMSCl promotes the Knoevenagel reactions through the activation of aldehydes resulting in electrophilic silylated intermediates **A** (Scheme 8). On the other hand, under the optimized reaction conditions, the methylene active components are likely to be converted to silylated compounds **B**–**E** containing double bonds susceptible to the addition of electrophile **A**. MP3 calculations suggest that in intermediates **F**–**I** trimethylsilyl and trimethylsyloxy groups form a coordination bond facilitating the elimination of hexamethyldisiloxane and HCl. The geometry of energy-optimized conformations of intermediates **F**–**I** correctly predict the configuration of unsymmetrical benzylidene products. It seems likely that the stereochemical requirements for the intramolecular coordination bond Si–O may be responsible

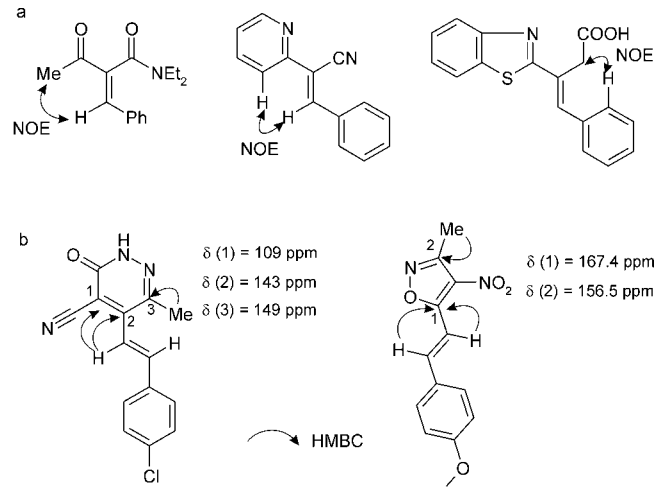
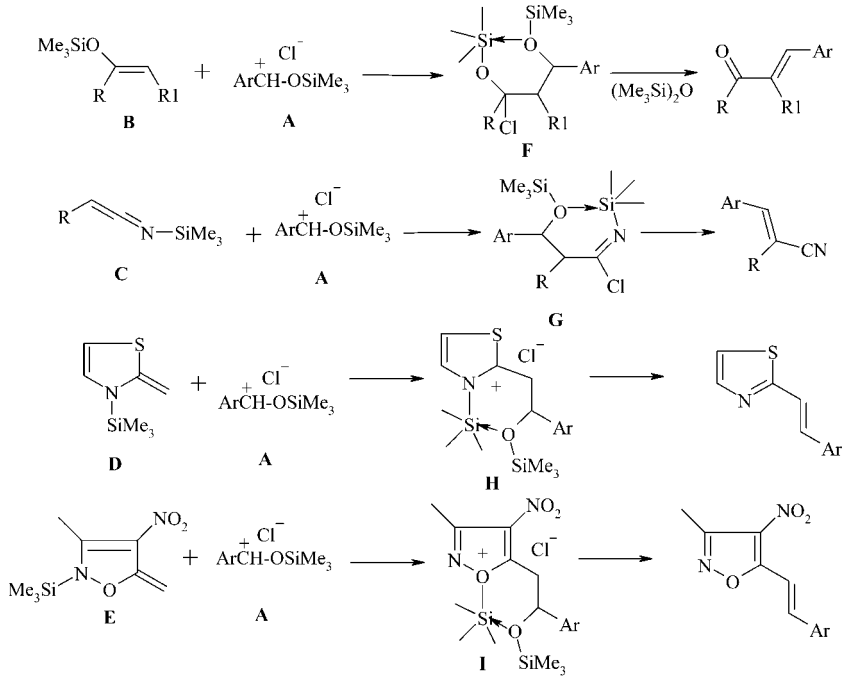


Figure 1. NMR structural studies of benzylidene derivatives: (a) NOE-correlations and (b) ^{1}H–^{13}C HMBC correlations. Signals were assigned on the basis of gated ^{13}C NMR spectra.

Scheme 8



for the selective formation of unsymmetrical benzylidene compounds.

Conclusion

In summary, an efficient methodology for the Knoevenagel-type condensation of various methylene active compounds with aromatic aldehydes was developed which allows for the obtaining of target compounds in nearly quantitative yields and >95 % purity. The optimized reaction conditions were used for the preparation of small libraries of benzylidene derivatives, which are promising building blocks for drug design, advanced materials, and agricultural chemistry. Overall, 11 000 benzylidene compounds have been synthesized in our laboratories (www.enamine.net) by parallel synthesis methods.

Experimental Section

General Remarks. All commercially unavailable starting materials were used without additional purification. All solvents were purified by standard methods. All procedures were carried out under an open atmosphere with no precautions taken to exclude ambient moisture. Melting points were measured with a Buchi melting points apparatus and are uncorrected. ^{1}H NMR (300, 400, and 500 MHz) spectra were recorded on Varian VXR-300, Varian Mercury-400, and Bruker Avance DRX 500 spectrometers with TMS as an internal standard. ^{13}C NMR (125 MHz) spectra were recorded on a Bruker Avance drx 500 spectrometer with TMS as an internal standard. LCMS spectra were recorded using chromatography/mass spectrometric system that consists of a high-performance liquid chromatograph "Agilent 1100 Series" equipped with a diode-matrix and mass-selective detector "Agilent LC/MSD SL". The parameters of chromatography–mass analysis are as follows. Column: Zorbax SB-C18, 1.8 μm, 4.6 mm × 15 mm. Solvents: A, acetonitrile/water (95:5), 0.1% TFA; B, water (0.1% of TFA). Eluent flow: 3 mL/sec. Volume of the injected sample: 1 μL. UV detectors were operated at 215, 254, and 265 nm. The ionization method was as follows: chemical ionization under atmospheric pressure. Ionization mode: simultaneous scanning of positive and negative ions in the mass range of 80–1000 *m*/*z*. According to the HPLC MS data, all of the synthesized compounds have a purity >95%. A BRANSON 2510E-MT ultrasonic bath was used.

All chemicals were obtained from commercially available sources and used without further purification (Aldrich, Fluka, and "Enamine LTD").

General Procedure. Methylene-active compounds **2**, **4**, **6**, **8**, **10**, **12**, **15**, **17**, and **19** (2 mmol) and the appropriate aromatic aldehyde **1** (2 mmol) were placed in a 15 mL pressure tube and dissolved in DMF (2–3 mL). Chlorotrimethylsilane (6 mmol) was added dropwise to the solution. The tube was thoroughly sealed and allowed to stand at 20 °C for 1–2 days or heated on a water bath for 2–24 h. After cooling, the flask was opened (*Caution! Excessive pressure inside*) and the reaction mixture was poured into water (15 mL) and allowed to stand at 20 °C in an ultrasonic bath for 1 h. The precipitate formed was filtered and washed with a small amount of *i*-PrOH to yield targeted compounds **3**, **5**, **7**, **9**, **11**, **13**, **16**, **18**, and **20** (see the Supporting Information).

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Supporting Information Available. Supplementary PDF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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