DOI: 10.1002/adsc.200900593

Trapping of Active Methylene Intermediates with Alkenes, Indoles or Thiols: Towards Highly Selective Multicomponent Reactions

Yanlong Gu,[a,*] Joël Barrault,[b] and François Jérôme[b,*]

[a] Institute of Physical Chemistry and Industrial Catalysis, Hubei Key Laboratory of Material Chemistry and Service Failure, School of Chemistry and Chemical Engineering, Huazhong University of Sciences and Technology, 1037# Luoyu Road, Hongshan Division, Wuhan, Hubei Province 430074, People's Republic of China
Fax: (+86)-(0)27-8754-4532; e-mail: klgyl@hust.edu.cn

[b] Laboratoire de Catalyse en Chimie Organique, Université de Poitiers/CNRS, 40 avenue du recteur, Pineau, 86022 Poitiers, France
E-mail: francois.jerome@univ-poitiers.fr

Received: August 28, 2009; Revised: October 23, 2009; Published online: December 11, 2009

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200900593.

Abstract: In this paper, a basic method to access new multicomponent reactions (MCRs) is reported. The mechanism of these MCRs is based on the trapping of methylene intermediates, formed *in situ* by reaction of formaldehyde with electron-rich carbons, with alkene, thiol or indole derivatives. According to our strategy, a wide range of valuable skeletons has been obtained in a one-pot reaction, thus allowing a minimization of waste, cost and labor. The presented methodology exhibits a broad substrate scope and electron-rich carbons in the α-position of a hydroxy or carbonyl group were found to be particularly efficient. More generally, this work offers new tools for creating molecular complexity and diversity from one of the simplest organic building blocks, formaldehyde.

Keywords: formaldehyde; methylene intermediates; multicomponent reaction; tandem reactions

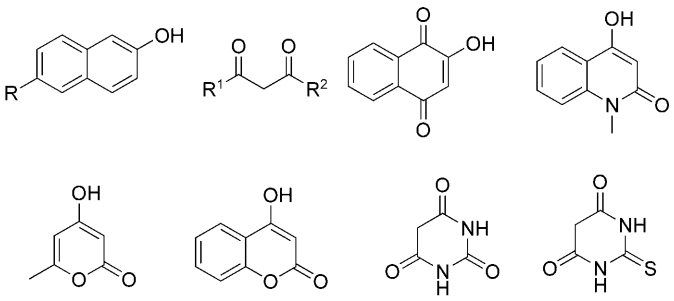
Introduction

With the aim of maximizing synthetic efficiency, complexity-generating diversity-oriented synthesis has gained more and more importance in organic synthesis.[1] In this context, multicomponent reactions (MCRs) are of prime importance and represent a promising tool to create molecular complexity in a one-step process.[2]

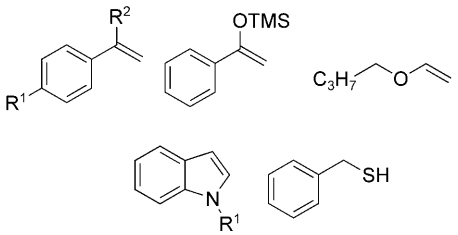
Formaldehyde is a very active substrate frequently used in MCRs.[3] Most of MCRs based on the utilization of formaldehyde involve fundamental reactions such as aldol and Mannich-type reactions. In most cases, the mechanism of these MCRs is based on the methylenation of electron-rich carbons with formaldehyde that generates active methylene compounds (or methides). These methylene compounds are then used as chemical platforms for the creation of various C–C, C–O, C–N bonds, among others. According to this strategy, complex molecules have been successfully synthesized in a one-pot reaction.[4] One of the most recent examples has been reported by Tietze and co-workers who successfully designed a novel three-component reaction involving nitroacetone, formaldehyde and alkyl vinyl ether for the total synthesis of (+)-D-forosamine.[5] In spite of these appealing results, MCRs based on the formation of methylene intermediates are still subject to strict limitations mainly because of (i) the poor substrate scope and (ii) the low selectivity of these MCRs. These two limitations mainly stem from the high reactivity of methylene intermediates which unfortunately causes a significant formation of side products. Therefore, up to now, only readily accessible and stable methylene intermediates are involved, thus explaining the poor substrate scope of these MCRs.

In this paper, we wish to report the ability of alkenes, indoles or thiols to selectively trap a wide range of *in situ* produced methylene intermediates, usually not eligible in conventional MCRs (Scheme 1). We will show here that, according to our methodology, a large library of complex molecules

Methylene precursors:



Trapping reagents:



Scheme 1. Substrates involved in this work.

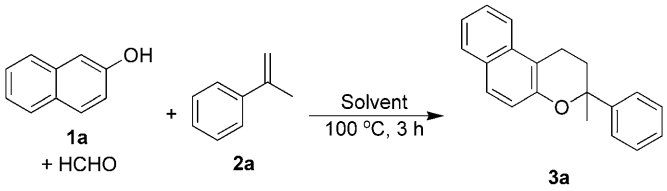
can be produced in fair to excellent yields, thus opening a new avenue to create molecular complexity and diversity from one of the simplest organic building block, formaldehyde.

Results and Discussion

In a first set of experiments, we investigated a three-component reaction involving 2-naphthol (**1a**), α-methylstyrene (**2a**) and formaldehyde (Table 1). Interestingly, after heating the reaction media at 100 °C in acetic acid, formation of a 2-substituted 5,6-benzochromane (**3a**) was clearly evidenced by means of NMR and GC/MS analyses (Table 1, entry 1).

Encouraged by this preliminary result, other solvents, such as water, glycerol, xylene, DMSO, DMF and an ionic liquid, [BMIm]BF_4 (1-butyl-3-methylimidazolium tetrafluoroborate), were then examined. In all cases, only a trace amount of product was obtained (Table 1, entries 2–7). Note that even the combination of these solvents with an acid or basic catalyst such as $InCl_3$, $Sc(OTf)_3$, $Bi(OTf)_3$, TsOH or NaOH did not significantly improve the reaction yield (Table 1, entries 8–12), thus illustrating the efficiency of acetic acid in this reaction. Utilization of formalin was also found to be crucial in this reaction since less than 5% yield of **3a** was obtained starting from paraformaldehyde (Table 1, entry 16). After optimization of the reaction parameters (100 °C, 3 h of reaction), **3a** was successfully isolated with 71% yield (Table 1, entry 1 and entries 13–18).

Table 1. Three-component reaction between 2-naphthol, formaldehyde and α-methylstyrene in different solvents.[a]

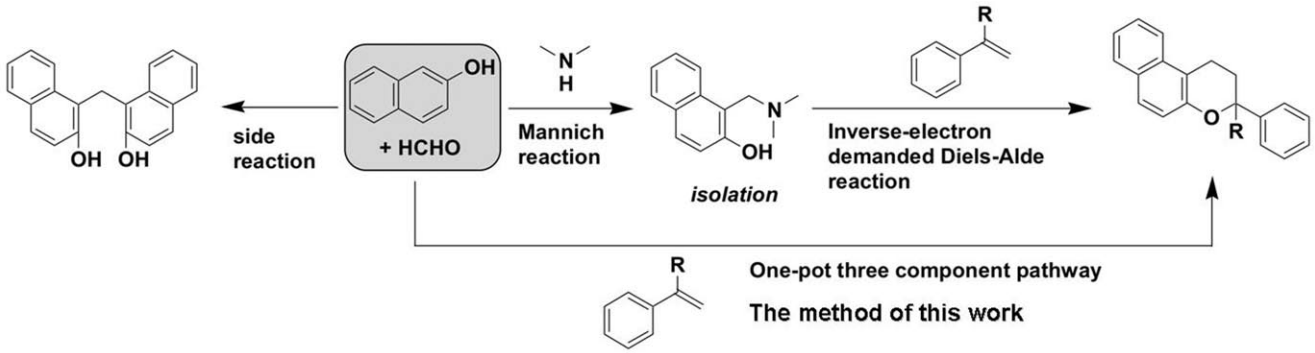


Entry	Solvent	Yield [%]
1	AcOH	71
2[b]	H_2O	<5
3	glycerol	<5
4	xylene	<5
5	DMSO	<5
6	DMF	14
7	[BMIm]BF_4	6
8	DMF ($InCl_3$)[i]	15
9	DMF ($Sc(OTf)_3$)[i]	7
10	DMF ($Bi(OTf)_3$)[i]	10
11	DMF (TsOH)[i]	11
12	DMF (NaOH)[i]	8
13[c]	AcOH	47
14[d]	AcOH	44
15[e]	AcOH	42
16[f]	AcOH	<5
17[g]	AcOH	26
18[h]	AcOH	24

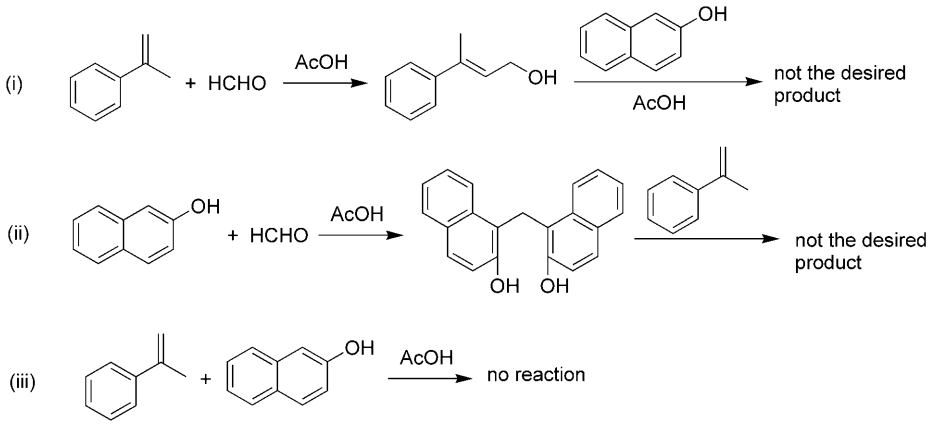
[a] Solvent: 1.5 mL, **1a**: 2.0 mmol, **2a**: 1 mmol, aqueous formaldehyde solution (37 wt%): 2.5 mmol.
[b] Temperature: 95 °C.
[c] Temperature: 115 °C.
[d] Temperature: 85 °C.
[e] Reaction time: 1 h.
[f] Paraformaldehyde was used.
[g] 1.0 equiv. **1a** was reused.
[h] 1.5 equiv. formaldehyde were used.
[i] 10 mol% catalyst were used.

2-Substituted 5,6-benzochromanes are important synthetic intermediates[6] that are generally synthesized according to a two-step reaction (Scheme 2).[7] The above-described, three-component reaction opens a new, efficient and straightforward way to synthesize 2-substituted 5,6-benzochromane derivatives in a one-pot procedure.

In order to understand the mechanism of this MCR, counter experiments were then carried out (Scheme 3**)**. First, α-methylstyrene and formaldehyde were mixed together at 100 °C in acetic acid [Scheme 3, pathway (i)]. Under these conditions, the formation of an allylic alcohol was observed. After addition of 2-naphthol, no formation of **3a** occurred. Next, we mixed 2-naphthol and formaldehyde in acetic acid [Scheme 3, pathway (ii)]. This time, we observed the formation of 1,1′-methylenebis-2-naphthalenol that was unable to further react with α-methylstyrene. Note that the formation of 1,1′-methylenebis-



Scheme 2. Synthesis of 2-substituted 5,6-benzochromanes from 2-naphthol and formaldehyde.



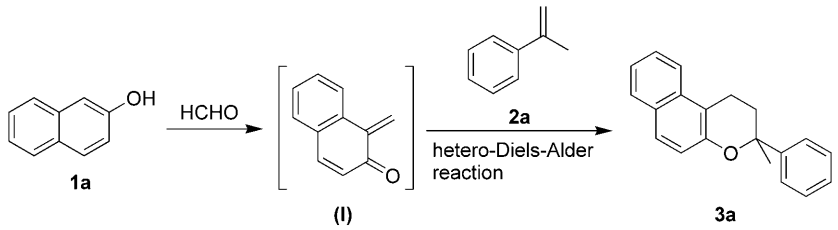
Scheme 3. Control experiments for understanding the mchanism of the three-component reaction of 2-naphthol, α-methylstyrene and formaldehyde.

2-naphthalenol[8] is also observed in our MCR, and it was inhibited using an excess of **1a** and formaldehyde (Table 1, entry 1). Finally, we found that no reaction occurred when 2-naphthol and α-methylstyrene were heated in acetic acid and in this case both reactants remained unaltered [Scheme 3, pathway (iii)] These three counter experiments suggest that the concomitant presence of 2-naphthol (**1a**), α-methylstyrene (**2a**) and formaldehyde in the same reaction pot is necessary for the selective formation of **3a**.

On the basis of our counter experiments and the existing literature, we suspect that the present MCR might proceed through a tandem reaction involving (i) condensation between **1a** and formaldehyde that generates the methylene intermediate (**I**) and (ii) a hetero-Diels–Alder reaction between (**I**) and **2a** to form the desired product **3a** (Scheme 4).

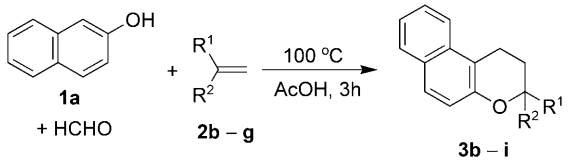
Note that this reaction mechanism is supported by the existing literature reports. The intermediate, *o*-quinone methide (**I**), which could be generated from 2-hydroxy-1-naphthalenemethanol in the presence of acid,[9] is known to be able to react with alkenes through a hetero-Diels–Alder reaction.[10]

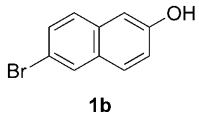
Interestingly, although the hetero-Diels–Alder reaction can theoretically yield two regioisomers, only one product was isolated in our case. For the moment, we are unable to discriminate between different parameters (solvent effect, steric hindrance, among others) to



Scheme 4. Plausible reaction pathway of the MCR.

Table 2. Three-component reaction between 2-naphthols, formaldehyde and styrenes in acetic acid.[a]



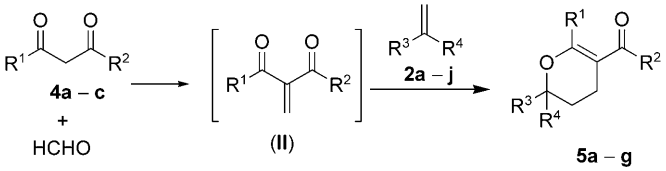


2b: R^1= C_6H_5, R^2 = H;
2c: R^1= 4-CH_3-C_6H_4, R^2 = H;
2d: R^1= 4-Cl-C_6H_4, R^2 = H;
2e: R^1= 4-*t*-Bu-C_6H_4, R^2 = H;
2f: R^1= 4-F-C_6H_4, R^2 = CH_3;
2g: R^1= 4-Cl-C_6H_4, R^2 = CH_3.

Entry	Phenol	Alkene	Product	Time [h]	Yield [%]
1[b]	**1a**	**2b**	**3b**	12.0	41
2	**1a**	**2c**	**3c**	3.0	68
3[b]	**1a**	**2d**	**3d**	12.0	30
4	**1a**	**2e**	**3e**	6.0	60
5	**1a**	**2f**	**3f**	3.0	70
6	**1a**	**2g**	**3g**	3.0	69
7[c]	**1b**	**2a**	**3h**	3.0	63
8	**1b**	**2f**	**3i**	4.0	64

[a] Solvent: 0.75 mL, **1a**: 1 mmol, alkene: 0.5 mmol, formaldehyde: 1.25 mmol.
[b] Temperature: 115 °C.
[c] Temperature: 85 °C.

Table 3. Three component reaction between 1,3-dicarbonyl compounds, formaldehyde and alkenes.[a]



4a: R^1 = Me, R^2 = OMe;
4b: R^1 = R^2 = Me;
4c: R^1 = OEt, R^2 = CH_2CO_2Et.

2i: R^3 = 4-MeO-C_6H_4, R4 = H;
2j: R^3 = C_6H_5, R^4 = OTMS.

Entry	1,3-Dicarbonyl	Alkene	Product	Time [h]	Yield [%]
1	**4a**	**2a**	**5a**	8.0	69
2	**4b**	**2a**	**5b**	8.0	78
3	**4c**	**2a**	**5c**	10.0	44
4	**4a**	**2c**	**5d**	6.0	66
5	**4a**	**2f**	**5e**	4.0	78
6	**4a**	**2i**	**5f**	4.0	83
7[b]	**4a**	**2j**	**5g**	2.0	41

[a] Formaldehyde: 1.5 mL, **2a**: 0.5 mmol, 1,3-dicarbonyl compound: 1 mmol, temperature: 80 °C.
[b] 50 °C.

explain this regioselectivity, and DFT calculations at the B3LYP/6-311++G** level are a topic of our current investigations.

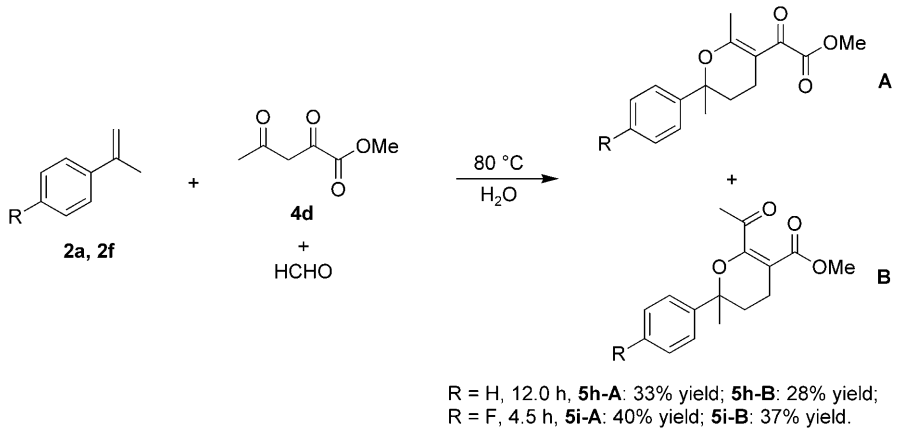
Having these first results in hand, various styrene derivatives were tested in this MCR (Table 2**)**. All styrene derivatives readily reacted with **1a** and formaldehyde in acetic acid affording the desired 2-substituted 5,6-benzochromanes **3b–g** in moderate to good yields (30–70% yield, Table 2, entries 1–6). The presence of an electron-donating group in the aromatic ring of substituted styrenes (**2c**–**e**) resulted in an increase of the reaction yield (entries 2 and 4). Styrenes with a methyl group in the α-position (**2f–g**) afforded better yields than those without substituents (entries 5 and 6). 6-Bromo-2-naphthol (**1b**) can also be used in this reaction but the yields of the products **3h** and **3i** are slightly lower (63%) than those obtained from **1a** (entries 7 and 8). As observed above, in all cases, only one regioisomer was obtained.

These promising results then encouraged us to investigate the possible assembling of other substrates with formaldehyde and alkenes. To our delight, commonly used chemicals such as 1,3-dicarbonyl compounds **4a–c**, were also able to selectively react with styrenes and formaldehyde, opening the access to a new type of three-component reaction (Table 3). In this case, the corresponding dihydropyran derivatives **5a–g** were isolated with 41–83% yields. Note that catalysts and expensive chemicals are usually required to build the skeleton of dihydropyran derivatives (see Supporting Information), thus showing the convenience of our methodology.[11]

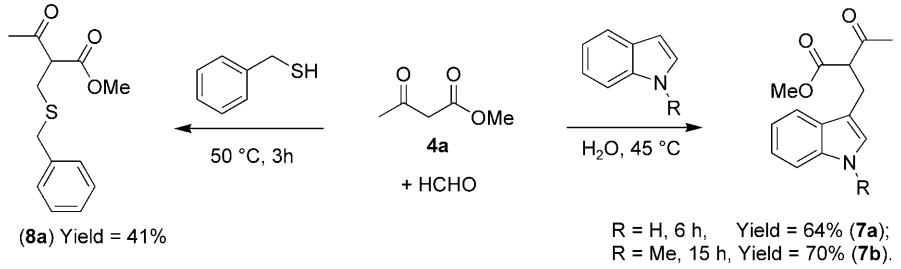
Inspired by the above-described mechanism, we assume that the reaction may involve here (i) a Knoevenagel reaction between the 1,3-dicarbonyl compound and formaldehyde to form the methylene intermediate (**II**) followed by (ii) a hetero-Diels–Alder reaction between (**II**) and the alkene to form the corresponding dihydropyran derivatives. This mechanism is also supported by a few previous reports.[12] It should be noted that, as observed above, only one regioisomer was still formed.

Interestingly, when methyl acetopyruvate (**4d**) was used as 1,3-dicarbonyl derivative in combination with formaldehyde and **2a** or **2f**, two products were obtained with similar yields (30–40%, Scheme 5).

Remarkably, indole and thiol derivatives were also able to trap the intermediate (**II**) through a (thio-)Michael reaction, thus affording two new MCRs (Scheme 6, see also Supporting Information). With this method, C-3-substituted functionalized indole derivatives that can be potentially used as tryptophan precursors,[13] were synthesized in 64–70% yields from three easily available starting materials. Previous methods reported for the synthesis of **7a** require more complex pathways, thus showing the convenience of our methodology (see Supporting Information).[14] Similarly, the three-component reaction involving a



Scheme 5. Three-component reaction involving styrenes, **4d** and formaldehyde.



Scheme 6. Three-component reactions between **4a**, formaldehyde and indoles or thiol.

thiol derivative afforded a thiomethylated 1,3-dicarbonyl derivative (**8a**) with 41% yield. Note that this methodology allowed overcoming either the traditional use of a stoichiometric amount of base or utilization of an expensive thiomethylation reagent like $ClCH_2SR$.[15]

Proceeding on the same line, we finally extended our strategy to more complex substrates in order to determine the scope of our methodology. Remarkably, as shown in Scheme 7, 2-hydroxy-1,4-naphthoquinone (**9a**), 4-hydroxy-6-methyl-2-pyrone (**9b**), barbituric acid (**9c**), 4,6-dihydroxy-2-mercaptopyrimidine (**9d**), 4-hydroxy-1-methyl-2-quinolone (**9e**) and 4-hydroxycoumarin (**9f**) also selectively reacted with formaldehyde and **2a** affording a diverse array of valuable and complex skeletons (51–90% yields) that find various applications. For instance, skeletons of **10a** and **10b** are active medicinal agents for the treatment of many diseases including erectile dysfunction and cancers (previously reported methods for the synthesis of these compounds are provided in the Supporting Information).[16] In addition, it should be noted that, for all reactions summarized in Scheme 7, only one regioisomer was still isolated. In all cases, the mechanism of these MCRs involves a methylenation of electron-rich carbons with formaldehyde that were then trapped by means of a hetero-Diels–Alder reactions with **2a**.

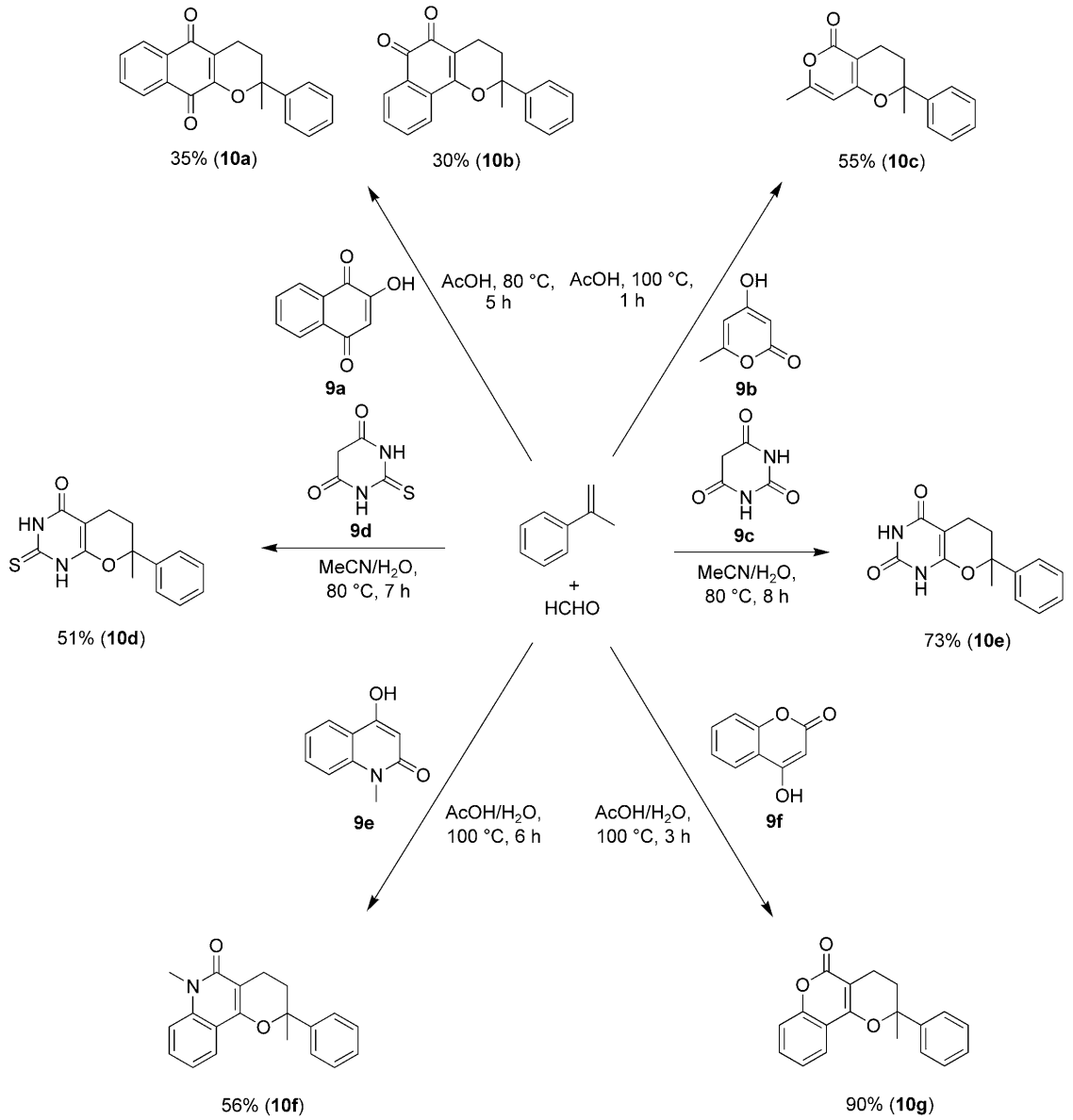
Conclusions

Through various examples, we showed here that formaldehyde is able to methylenate a large variety of electron-rich carbons, thus allowing the convenient synthesis of many organic skeletons in a one-pot reaction. The reported MCRs are capable of affording highly valuable derivatives that are usually synthesized by multi-step reactions. It is also noteworthy that there are many possibilities to further extend this method, in particular using other trapping reagents or electron-rich carbons. Further studies are underway in our groups.

Experimental Section

General Procedure

All reactions were conducted in a V-type flask of 10-mL equipped with a triangle magnetic stirring bar. In a typical reaction, acetic acid (1.5 mL) was mixed with 2-naphthol (288 mg, 2.0 mmol), formalin (37 wt%, 203 mg, 2.5 mmol) and *a*-methylstyrene (118 mg, 1.0 mmol) under air. The mixture was stirred for 3 h at 100 °C. After completion of the reaction, a white solid was formed. The reaction mixture was then poured into ethyl acetate (3 mL) and neutralized with an aqueous solution of NaOH (2 N). The upper organic phase was separated, and the bottom aqueous phase was ex-



Scheme 7. Three-component reactions from formaldehyde and **2a**.

tracted twice with 2 mL of ethyl acetate. All organic phases were then combined, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The desired products were purified by preparative TLC. Note that reactions involving 2-hydroxy-1,4-naphthoquinone, 4-hydroxy-1-methyl-2-quinolone and 4-hydroxy-6-methyl-2-pyrone were conducted using a similar procedure. Reactions involving 1,3-dicarbonyl compounds were conducted in water. More details are provided in the Supporting Information.

Physicochemical Characterizations of the Reaction Products

2,3-Dihydro-3-methyl-3-phenyl-1*H*-naphtho[2,1-*b*]pyran (3a):[7b] White solid, mp 98–100 °C; yield: 71% (ethyl acetate/petroleum ether = 1/4), ^{1}H NMR ($CDCl_3$): δ = 1.65 (s, 3H), 2.14 (ddd, J_a = 5.6 Hz, J_b = 10.0 Hz, J_c = 15.6 Hz, 1H), 2.48 (ddd, J_a = 4.4 Hz, J_b = 6.0 Hz, J_c = 14.0 Hz, 1H), 2.58 (ddd, J_a = 6.0 Hz, J_b = 10.0 Hz, J_c = 16.0 Hz, 1H), 2.96 (dt, J_a = 5.2 Hz, J_b = 16.8 Hz, 1H), 7.08–7.16 (m, 1H), 7.19–7.28 (m, 4H), 7.35–7.39 (m, 3H), 7.64 (t, J = 7.2 Hz, 2H), 7.70 (d, J = 8.0 Hz, 1H); ^{13}C NMR: δ = 19.5, 30.1, 32.7, 78.3, 113.4, 119.5, 122.1, 123.2, 125.0, 126.3, 126.9, 128.0, 128.5, 129.0, 133.1, 145.5, 151.6.

2,3-Dihydro-3-phenyl-1*H*-naphtho[2,1-*b*]pyran (3b):[7c] White solid, mp 82–84 °C; yield: 41% (ethyl acetate/petroleum ether = 1/4), ^{1}H NMR ($CDCl_3$): δ = 2.12–2.23 (m,1H), 2.25–2.33 (m, 1H), 2.34 (s, 3H), 3.09 (dd, J_a = 4.4 Hz, J_b = 8.0 Hz, 2H), 5.03 (dd, J_a = 2.0 Hz, J_b = 12.4 Hz, 1H), 7.12 (d, J = 8.8 Hz, 1H), 7.18 (d, J = 7.6 Hz, 2H), 7.32 (t, J = 8.0 Hz, 3H), 7.46 (t, J = 8.0 Hz, 1H), 7.61 (d, J = 8.8 Hz, 1H), 7.75 (dd, J_a = 8.4 Hz, J_b = 12.4 Hz, 2H); ^{13}C NMR: δ = 21.3, 21.9, 29.7, 77.5, 113.7, 119.4, 122.1, 123.3, 126.2, 126.4, 127.8, 128.5, 129.1, 129.3, 133.1, 137.7, 138.7, 152.9.

3-(4-Methylphenyl)-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran (3c):[7e] White solid, mp 110–112 °C; yield: 68% (ethyl acetate/petroleum ether = 1/5), ^{1}H NMR ($CDCl_3$): δ = 2.12–2.24 (m,1 H), 2.30–2.39 (m, 1 H), 3.07–3.14 (m, 2 H), 5.08 (dd, J_a = 2.0 Hz, J_b = 10.4 Hz, 1 H), 7.14 (d, J = 8.8 Hz, 1 H), 7.32 (dd, J_a = 8.0 Hz, J_b = 16.0 Hz, 2 H), 7.38 (t, J = 7.2 Hz, 2 H), 7.42–7.49 (m, 3 H), 7.62 (d, J = 8.8 Hz, 1 H), 7.77 (dd, J_a = 8.4 Hz, J_b = 12.4 Hz, 2 H); ^{13}C NMR: δ = 21.8, 29.8, 77.5, 113.7, 119.3, 122.1, 123.4, 126.2, 126.4, 127.9, 128.5, 128.6, 129.1, 133.1, 141.6, 152.8.

3-(4-Chlorophenyl)-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran (3d):[7e] White solid, mp 142–144 °C; yield: 30% (ethyl acetate/petroleum ether = 1/4), ^{1}H NMR ($CDCl_3$): δ = 2.04–2.16 (m, 1 H), 2.26–2.35 (m, 1 H), 3.04–3.11 (m, 2 H), 5.02 (dd, J_a = 2.4 Hz, J_b = 10.4 Hz, 1 H), 7.07 (d, J = 9.2 Hz, 1 H), 7.27–7.36 (m, 5 H), 7.43 (t, J = 7.2 Hz, 1 H), 7.59 (d, J = 8.8 Hz, 1 H), 7.73 (t, J = 8.8 Hz, 2 H); ^{13}C NMR: δ = 21.6, 29.7, 76.8, 113.5, 119.1, 122.0, 123.5, 126.5, 127.5, 127.9, 128.5, 128.7, 129.1, 133.0, 133.6, 140.1, 152.4.

3-(4-*tert*-Butylphenyl)-2,3-dihydro-1*H*-Naphtho[2,1-*b*]pyran (3e): White solid, mp 122–124 °C, yield: 60% (ethyl acetate/petroleum ether = 1/6), ^{1}H NMR ($CDCl_3$): δ = 1.36 (s, 9 H), 2.15–2.27 (m, 1 H), 2.31–2.38 (m, 1 H), 3.11 (dd, J_a = 4.8 Hz, J_b = 8.0 Hz, 2 H), 5.05 (dd, J_a = 2.0 Hz, J_b = 10.4, 1 H), 7.13 (d, J = 8.8 Hz, 1 H), 7.32 (t, J = 8.0 Hz, 1 H), 7.40 (dd, J_a = 8.8 Hz, J_b = 10.8 Hz, 4 H), 7.46 (t, J = 8.0 Hz, 1 H), 7.61 (d, J = 8.8 Hz, 1 H), 7.77 (dd, J_a = 8.8 Hz, J_b = 15.2 Hz, 2 H); ^{13}C NMR: δ = 21.9, 29.5, 31.5, 34.7, 77.5, 113.7, 119.4, 122.1, 123.3, 125.6, 126.1, 126.4, 127.8, 128.5, 129.1, 133.1, 138.5, 151.0, 152.9; IR: ν = 2948, 2868, 1620, 1597, 1512, 1465, 1396, 1360, 1261, 1237, 1175, 1108, 1067, 993, 972, 904, 861, 818, 768, 741, 572 cm^{-1}; anal. calcd. for $C_{23}H_{24}O$: C 87.30, H 7.64; found: C 87.44, H 7.71.

3-(4-Fluorophenyl)-3-methyl-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran (3f): Colorless liquid; Yield: 70% (ethyl acetate/petroleum ether = 1/4), ^{1}H NMR ($CDCl_3$): δ = 1.60 (s, 3 H), 2.09 (ddd, J_a = 6.0 Hz, J_b = 10.4 Hz, J_c = 13.6 Hz, 1 H), 2.37 (dt, J_a = 4.8 Hz, J_b = 13.6 Hz, 1 H), 2.55 (ddd, J_a = 6.0 Hz, J_b = 10.0 Hz, J_c = 20.4 Hz, 1 H), 2.93 (dt, J_a = 4.8 Hz, J_b = 16.4 Hz, 1 H), 6.88 (dt, J_a = 2.4 Hz, J_b = 8.8 Hz, 2 H), 7.20 (dd, J_a = 4.4 Hz, J_b = 9.2 Hz, 1 H), 7.22–7.34 (m, 3 H), 7.38 (t, J = 8.8 Hz, 1 H), 7.63 (t, J = 8.4 Hz, 2 H), 7.69 (t, J = 8.0 Hz, 1 H); ^{13}C NMR: δ = 19.5, 30.0, 32.8, 77.9, 113.5, 115.2, 115.4, 119.5, 122.1, 123.4, 126.4, 126.8, 126.8, 128.2, 128.6, 129.1, 133.1, 141.2, 141.3, 151.4, 160.6, 163.0; IR: ν = 3062, 2977, 2929, 2847, 1603, 1510, 1466, 1435, 1396, 1319, 1266, 1234, 1160, 1108, 1092, 1015, 965, 921, 888, 868, 835, 812, 771, 746, 687 cm^{-1}; anal. calcd. for $C_{20}H_{17}FO$: C 82.17, H 5.86; found: C, 82.24, H 5.81.

3-(4-Chlorophenyl)-3-methyl-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran (3g): Colorless liquid, yield: 69% (ethyl acetate/petroleum ether = 1/4), ^{1}H NMR ($CDCl_3$): δ = 1.62 (s, 3 H), 2.13 (ddd, J_a = 5.6 Hz, J_b = 10.6 Hz, J_c = 16.0 Hz, 1 H), 2.42 (ddd, J_a = 4.4 Hz, J_b = 5.6 Hz, J_c = 13.6 Hz, 1 H), 2.57 (ddd, J_a = 6.0 Hz, J_b = 10.0 Hz, J_c = 16.4 Hz, 1 H), 2.96 (dt, J_a = 5.2 Hz, J_b = 16.8 Hz, 1 H), 7.19 (dd, J_a = 3.2 Hz, J_b = 9.2 Hz, 3 H), 7.25–7.32 (m, 3 H), 7.39 (t, J = 7.2 Hz, 1 H), 7.64 (dd, J_a = 5.2 Hz, J_b = 8.0 H, 2 H), 7.71 (d, J = 8.0 Hz, 1 H); ^{13}C NMR: δ = 19.4, 29.9, 32.6, 77.9, 113.4, 119.3, 122.0, 123.4, 126.4, 126.6, 128.1, 128.5, 128.6, 129.0, 132.6, 133.0, 144.0, 151.3; IR: ν = 2926, 1618, 1594, 1508, 1485, 1465, 1433, 1395, 1264, 1235, 1159, 1111, 1088, 1009, 975, 817, 745, 685 cm^{-1}; anal. calcd. for $C_{20}H_{17}ClO$: C 77.79, H 5.55; found: C 77.69, H 5.46.

8-Bromo-3-methyl-3-phenyl-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran (3h): White solid, mp 68–70 °C; yield: 63% (ethyl acetate/petroleum ether = 1/3), ^{1}H NMR ($CDCl_3$): δ = 1.66 (s, 3 H), 2.08–2.20 (m, 1 H), 2.45–2.60 (m, 2 H), 2.89 (dt, J_a = 4.0 Hz, J_b = 16.4 Hz, 1 H), 7.17 (t, J = 7.2 Hz, 1 H), 7.25 (dd, J_a = 7.6 Hz, J_b = 15.6 Hz, 3 H), 7.35–7.52 (m, 5 H), 7.82 (s, 1 H); ^{13}C NMR: δ = 19.4, 30.1, 32.5, 78.4, 113.8, 116.8, 120.6, 123.9, 124.9, 127.0, 127.1, 128.5, 129.3, 130.1, 130.3, 131.5, 145.2, 151.8; IR: ν = 2975, 2927, 1617, 1587, 1497, 1462, 1445, 1392, 1354, 1313, 1264, 1238, 1184, 1163, 1104, 1071, 1027, 962, 874, 807, 762, 699, 598 cm^{-1}; anal. calcd. for $C_{20}H_{17}BrO$: C 68.00, H 4.85; found: C 68.11, H 4.73.

8-Bromo-3-(4-fluorophenyl)-3-methyl-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran (3i): Gum-like liquid; yield: 64% (ethyl acetate/petroleum ether = 1/3), ^{1}H NMR ($CDCl_3$): δ = 1.62 (s, 3 H), 2.12 (ddd, J_a = 5.6 Hz, J_b = 10.0 Hz, J_c = 16.0 Hz, 1 H), 2.43 (dt, J_a = 4.4 Hz, J_b = 13.6 Hz, 1 H), 2.54 (ddd, J_a = 6.0 Hz, J_b = 10.4 Hz, J_c = 16.8 Hz, 1 H), 2.90 (dt, J_a = 5.2 Hz, J_b = 16.4 Hz, 1 H), 6.92 (t, J = 8.8 Hz, 2 H), 7.19 (d, J = 8.8 Hz, 1 H), 7.31 (dd, J_a = 5.6 Hz, J_b = 8.8 Hz, 2 H), 7.46 (ddd, J_a = 2.8 Hz, J_b = 8.8 Hz, J_c = 20.8 Hz, 3 H), 7.82 (d, J = 2.0 Hz, 1 H); ^{13}C NMR: δ = 19.3, 29.9, 32.5, 78.0, 113.6, 115.2, 115.4, 116.9, 120.4, 123.8, 126.6, 126.7, 127.2, 129.4, 130.1, 130.3, 131.5, 140.9, 140.9, 151.6, 160.5, 162.9; IR: ν = 3062, 2977, 2929, 2849, 1593, 1505, 1459, 1392, 1355, 1314, 1263, 1235, 1160, 1109, 1095, 1079, 1015, 962, 871, 835, 808, 731, 593 cm^{-1}; anal. calcd. for $C_{20}H_{16}BrFO$: C 64.71, H 4.34; found: C 64.86, H 4.30.

2,6-Dimethyl-3-methoxycarbonyl-6-phenyl-5,6-dihydropyran (5a): Colorless liquid, yield: 69% (heptane/ethyl acetate: 4/1), ^{1}H NMR: δ = 1.54 (s, 3 H), 1.79–1.98 (m, 2 H), 2.05–2.24 (m, 1 H), 2.25–2.37 (m, 1 H), 2.39 (s, 3 H), 3.62 (s, 3 H), 7.12–7.29 (m, 3 H), 7.29–7.35 (t, J = 8.0 Hz, 2 H); ^{13}C NMR: δ = 19.5, 20.5, 29.3, 32.4, 50.9, 79.5, 100.9, 124.3, 127.0, 128.5, 144.9, 163.7, 168.8; IR: ν = 2978, 2948, 1706, 1621, 1446, 1434, 1379, 1296, 1278, 1264, 1233, 1186, 1165, 1094, 1086, 1073, 1028, 1012, 957, 762, 698 cm^{-1}; HR-MS (ESI): m/z = 247.3097, calcd. for $C_{15}H_{18}O_3$, [M + H$^+$]: 247.3096.

3-Acyl-2,6-dimethyl-6-phenyl-5,6-dihydropyran (5b): Colorless liquid, yield: 78% (heptane/ethyl acetate: 2/1), ^{1}H NMR: δ = 1.55 (s, 3 H), 1.85–2.08 (m, 2 H), 2.11 (s, 3 H), 2.15–2.33 (m, 2 H), 2.37 (s, 3 H), 7.19–7.27 (m, 3 H), 7.32–7.36 (m, 2 H); ^{13}C NMR: δ = 20.8, 21.3, 29.4, 29.5, 32.6, 79.3, 109.6, 124.2, 127.0, 128.5, 144.7, 163.2, 198.8; IR: ν = 2980, 2929, 2966, 1668, 1567, 1446, 1375, 1284, 1095, 1073, 945, 766, 699 cm^{-1}; HR-MS (ESI): m/z = 230.3109, calcd. for $C_{15}H_{18}O_2$, [M]: 230.3022.

3-Ethoxycarbonyl-2-[(Ethoxycarbonyl)methyl]-6-methyl-6-phenyl-5,6-dihydropyran (5c): Colorless liquid, yield: 44% (ethyl acetate/petroleum ether = 1/3), ^{1}H NMR ($CDCl_3$): δ = 1.23 (t, J = 7.2 Hz, 3 H), 1.28 (t, J = 7.2 Hz, 3 H), 1.58 (s, 3 H), 1.92 (ddd, J_a = 6.4 Hz, J_b = 8.0 Hz, J_c = 13.6 Hz, 1 H), 2.02–2.18 (m, 2 H), 2.39 (dt, J_a = 2.0 Hz, J_b = 16.8 Hz, 1 H), 3.78 (d, J = 16.4 Hz, 1 H), 3.90 (d, J = 16.4 Hz, 1 H), 4.11 (ddd, J_a = 1.2 Hz, J_b = 6.8 Hz, J_c = 14.0 Hz, 2 H), 4.20 (q, J = 7.2 Hz, 2 H), 7.23–7.28 (m, 1 H), 7.32–7.40 (m, 4 H); ^{13}C NMR: δ = 14.2, 14.3, 19.5, 28.2, 32.7, 40.1, 59.9, 60.8, 80.2, 103.5, 124.4, 127.1, 128.4, 144.9, 158.9, 167.7, 169.8; IR: ν = 2981, 2934, 1741, 1699, 1628, 1448, 1371, 1265, 1164, 1097, 1030, 969,

852, 764, 701 cm^{-1}; HRMS (ESI): $m/z = 332.3901$, calcd. for $C_{19}H_{24}O_5$ [M]: 332.3909.

2-Methyl-3-methoxycarbonyl-6-(4-methylphenyl)-5,6-dihydropyran (5d): Colorless liquid, yield: 66% (ethyl acetate/petroleum ether = 1/4), ^1H NMR ($CDCl_3$): $\delta = 1.74$–1.85 (m, 1H), 1.99–2.06 (m, 1H), 2.25 (s, 3H), 2.29 (s, 3H), 2.30–2.43 (m, 2H), 3.65 (s, 3H), 4.77 (dd, $J_a = 2.4$ Hz, $J_b = 10.4$, 1H), 7.11 (d, $J = 8.0$ Hz, 2H), 7.16 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR: $\delta = 20.4$, 21.2, 21.9, 29.1, 51.0, 78.1, 101.2, 125.9, 129.2, 137.8, 137.8, 165.3, 169.0; IR: $\nu = 3014$, 2949, 2925, 2857, 1706, 1623, 1517, 1435, 1381, 1355, 1273, 1209, 1185, 1132, 1083, 1017, 958, 884, 813, 762 cm^{-1}; HR-MS (ESI): $m/z = 246.3019$, calcd. for $C_{15}H_{18}O_3$ [M]: 246.3016.

2,6-Dimethyl-3-methoxycarbonyl-6-(4-fluorophenyl)-5,6-dihydropyran (5e): Colorless liquid; yield: 78% (ethyl acetate/petroleum ether = 1/4), ^1H NMR ($CDCl_3$): $\delta = 1.44$ (s, 3H), 1.75–1.90 (m, 2H), 2.03–2.30 (m, 1H), 2.29 (s, 3H), 3.56 (s, 3H), 6.92 (t, $J = 8.8$ Hz, 2H), 7.12–7.19 (m, 2H); ^{13}C NMR: $\delta = 19.4$, 20.4, 29.3, 32.4, 50.9, 79.1, 100.9, 115.1, 115.3, 126.0, 126.1, 140.7, 140.7, 160.5, 163.0, 163.5, 168.7; IR: $\nu = 2980$, 2949, 2932, 2878, 1707, 1623, 1510, 1435, 1379, 1358, 1298, 1280, 1264, 1231, 1189, 1163, 1094, 1013, 992, 958, 881, 859, 836, 814, 793, 768, 726, 678, 635, 600, 586, 551 cm^{-1}; HR-MS (ESI): $m/z = 264.2892$, calcd. for $C_{15}H_{11}FO_3$ [M]: 264.2921.

2-Methyl-3-methoxycarbonyl-6-(4-methoxyphenyl)-5,6-dihydropyran (5f): White solid, mp 56–58 °C; yield: 83% (ethyl acetate/petroleum ether = 1/4), ^1H NMR ($CDCl_3$): $\delta = 1.71$–1.83 (m, 1H), 1.95–2.04 (m, 1H), 2.22 (s, 3H), 2.23–2.43 (m, 2H), 3.63 (s, 3H), 3.72 (s, 3H), 4.72 (d, $J = 8.8$ Hz, 1H), 6.81 (d, $J = 8.4$ Hz, 2H), 7.17 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR: $\delta = 20.4$, 22.0, 29.1, 51.0, 55.3, 78.0, 101.1, 113.9, 127.3, 132.9, 156.4, 165.3, 169.0; IR: $\nu = 2999$, 2952, 2840, 1709, 1620, 1516, 1461, 1437, 1381, 1357, 1275, 1249, 1209, 1180, 1133, 1083, 1034, 1015, 958, 882, 830, 764, 589 cm^{-1}; HRMS (ESI): $m/z = 262.2981$, calcd. for $C_{15}H_{18}O_4$ [M]: 262.3010.

2-Methyl-3-methoxycarbonyl-6-phenyl-6-trimethylsiloxy-5,6-dihydropyran (5g): Colorless liquid, yield: 41% (petroleum ether/ethyl acetate: 5/1), ^1H NMR ($CDCl_3$): $\delta = 0.00$ (s, 9H), 1.61–1.70 (m, 1H), 2.07–2.14 (m, 1H), 2.33–2.41 (m, 1H), 2.43 (s, 3H), 2.45–2.55 (m, 1H), 3.77 (s, 1H), 7.32–7.42 (m, 3H), 7.48–7.53 (m, 2H); ^{13}C NMR: $\delta = 1.1$, 18.7, 20.3, 35.7, 51.1, 99.6, 102.3, 125.3, 127.9, 128.0, 144.4, 161.9, 168.7; IR: $\nu = 2956$, 1713, 1634, 1436, 1382, 1347, 1279, 1255, 1224, 1189, 1162, 1127, 1083, 1061, 1023, 997, 911, 883, 867, 844, 760, 700 cm^{-1}; HRMS (ESI): $m/z = 320.4532$, calcd. for $C_{17}H_{24}O_4Si$ [M]: 320.4556.

Methyl 3,4-dihydro-α-oxo-2,6-dimethyl-6-phenyl-2*H*-pyran-5-acetate (5h-A): Colorless liquid, yield: 33% (petroleum ether/ethyl acetate = 3/1), ^1H NMR ($CDCl_3$): $\delta = 1.52$ (s, 3H), 1.81–1.97 (m, 2H), 2.10–2.18 (m, 1H), 2.20–2.28 (m, 1H), 2.27 (s, 3H), 3.74 (s, 3H), 7.15–7.22 (m, 3H), 7.27 (t, $J = 8.0$ Hz, 2H), ^{13}C NMR: $\delta = 18.4$, 20.7, 29.0, 32.2, 52.3, 81.3, 106.6, 124.1, 127.4, 128.6, 144.1, 166.6, 169.3, 186.7; IR: $\nu = 2980$, 2954, 2933, 2856, 1739, 1668, 1592, 1566, 1497, 1447, 1381, 1320, 1260, 1207, 1162, 1123, 1085, 1063, 1029, 992, 917, 764, 736, 701 cm^{-1}; HR-MS (ESI): $m/z = 274.3132$, calcd. for $C_{16}H_{18}O_4$ [M]: 274.3117.

2-Acyl-3-methoxycarbonyl-6-phenyl-5,6-dihydropyran (5h-B): Colorless liquid, yield: 28% (petroleum ether/ethyl acetate = 3/1), ^1H NMR ($CDCl_3$): $\delta = 1.53$ (s, 3H), 1.85–1.97 (m, 2H), 2.02 (s, 3H), 2.22–2.34 (m, 2H), 3.83 (s, 3H), 7.17–7.23 (m, 1H), 7.24–7.29 (m, 4H); ^{13}C NMR: $\delta = 19.9$, 28.1, 29.4, 31.8, 52.9, 81.0, 114.4, 124.3, 127.4, 128.7, 143.4, 150.9, 164.9, 198.2; IR: n = 2980, 2952, 2933, 1745, 1686, 1598, 1442, 1369, 1299, 1286, 1269, 1218, 1172, 1087, 1073, 1032, 966, 943, 907, 867, 759, 702, 650 cm^{-1}; HR-MS (ESI): $m/z = 274.3102$, calcd. for $C_{16}H_{18}O_4$ [M]: 274.3117.

Methyl 3,4-dihydro-α-oxo-2,6-dimethyl-6-(4-fluorophenyl)-2*H*-pyran-5-acetate (5i-A): Colorless liquid, yield: 40% (petroleum ether/ethyl acetate = 4/1); ^1H NMR ($CDCl_3$): $\delta = 1.58$ (s, 3H), 2.09–2.17 (m, 2H), 2.19 (dt, $J_a = 4.4$ Hz, $J_b = 12.4$ Hz, 1H), 2.29–2.38 (m, 1H), 2.34 (s, 3H), 3.83 (s, 3H), 7.03 (t, $J = 8.8$ Hz, 2H), 7.23 (dd, $J_a = 5.2$ Hz, $J_b = 8.8$ Hz, 2H); ^{13}C NMR: $\delta = 18.4$, 20.7, 28.9, 32.2, 52.3, 80.8, 106.6, 115.3, 115.6, 125.9, 126.0, 139.9, 140.0, 160.6, 163.1, 166.5, 169.0, 186.7; IR: $\nu = 2981$, 2954, 2934, 2857, 1739, 1668, 1595, 1512, 1450, 1382, 1320, 1261, 1232, 1208, 1162, 1122, 1067, 992, 917, 837, 735 cm^{-1}; HR-MS (ESI): $m/z = 292.3068$, calcd. for $C_{16}H_{17}FO_4$ [M]: 292.3022.

2-Acyl-3-methoxycarbonyl-6-(4-fluorophenyl)-5,6-dihydropyran (5i-B): White solid, mp 78–80 °C, yield: 37% (petroleum ether/ethyl acetate = 4/1); ^1H NMR ($CDCl_3$): $\delta = 1.05$ (s, 3H), 1.84–1.97 (m, 2H), 2.04 (s, 3H), 2.18–2.27 (m, 1H), 2.27–2.35 (m, 1H), 3.82 (s, 3H), 6.96 (dt, $J_a = 2.0$ Hz, $J_b = 8.4$ Hz, 2H), 7.25 (ddd, $J_a = 2.0$ Hz, $J_b = 4.0$ Hz, $J_c = 6.8$ Hz, 2H); ^{13}C NMR: $\delta = 19.8$, 28.1, 29.4, 31.8, 52.9, 80.6, 114.5, 115.4, 115.6, 126.1, 126.2, 139.2, 139.2, 150.5, 160.7, 163.1, 164.8, 198.2; IR: $\nu = 2991$, 2957, 2898, 1747, 1676, 1589, 1511, 1457, 1430, 1375, 1300, 1233, 1170, 1114, 1087, 1032, 968, 945, 869, 840, 749, 656 cm^{-1}; HR-MS (ESI): $m/z = 292.3047$, calcd. for $C_{16}H_{17}FO_4$ [M]: 292.3022.

Methyl α-acetyl-1*H*-indole-3-propanoate (7a):[14e] Colorless liquid, yield: 64% (heptane/ethyl acetate = 4/1), ^1H NMR ($CDCl_3$): $\delta = 2.08$ (s, 3H), 3.25 (d, $J = 7.7$ Hz, 2H), 3.60 (s, 3H), 3.86 (t, $J = 7.5$ Hz, 1H), 6.86 (d, $J = 2.3$ Hz, 1H), 7.00–7.17 (m, 2H), 7.23 (dd, $J_a = 6.6$ Hz, $J_b = 10.0$ Hz, 1H), 7.50 (d, $J = 7.7$ Hz, 1H), 8.12 (bs, 1H); ^{13}C NMR: $\delta = 22.9$, 28.6, 51.4, 59.0, 110.3, 110.8, 117.4, 118.4, 121.1, 121.6, 125.9, 135.1, 169.0, 202.4.

Methyl α-acetyl-(1-methylindol-3-yl)-3-propanoate (7b): Colorless liquid, yield: 70% (heptane/ethyl acetate = 4/1), ^1H NMR ($CDCl_3$): $\delta = 2.08$ (s, 3H), 3.23 (d, $J = 7.5$ Hz, 2H), 3.60 (s, 6H), 3.82 (t, $J = 7.5$ Hz, 1H), 6.75 (s, 1H), 7.02 (td, $J_a = 6.8$ Hz, $J_b = 10.4$ Hz, 1H), 7.08–7.22 (m, 2H), 7.48 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR: $\delta = 22.8$, 28.6, 31.6, 51.4, 59.2, 108.3, 109.5, 117.5, 117.9, 120.6, 126.3, 135.9, 168.9, 202.1; IR: $\nu = 2952$, 1704, 1713, 1473, 1435, 1357, 1325, 1250, 1221, 1200, 1147, 1012, 738 cm^{-1}; HR-MS (ESI): $m/z = 260.3091$, calcd. for $C_{15}H_{17}NO_3$ [M + H$^+$]: 260.3083.

Methyl 3-oxo-2-[(benzylthio)methyl]-butanate (8a): Colorless liquid, yield: 41% (petroleum ether/ethyl acetate = 4/1); ^1H NMR ($CDCl_3$): $\delta = 2.20$ (s, 3H), 2.88 (d, $J = 7.6$ Hz, 2H), 3.58 (t, $J = 7.6$ Hz, 1H), 3.73 (s, 2H), 3.74 (s, 3H), 7.23–7.29 (m, 1H), 7.29–7.36 (m, 4H); ^{13}C NMR: $\delta = 28.8$, 29.6, 36.8, 52.7, 59.4, 127.3, 128.7, 128.9, 137.8, 168.8, 201.5; IR: $\nu = 3061$, 3028, 3005, 2953, 2924, 2848, 1745, 1645, 1616, 1494, 1437, 1359, 1254, 1214, 1148, 1070, 1026, 993, 771, 704 cm^{-1}; HR-MS (ESI): $m/z = 252.3341$, calcd. for $C_{13}H_{16}O_3S$ [M]: 252.3303.

3,4-Dihydro-2-methyl-2-phenyl-2*H*-naphtho[2,3-*b*]pyran-5,10-dione (10a): Yellow solid, mp 138–140 °C, yield: 35% (petroleum ether/ethyl acetate = 2/1); ^1H NMR ($CDCl_3$): $\delta =$

1.65 (s, 3H), 1.15–2.15 (s, 1H), 2.06–2.17 (m, 1H), 2.40 (ddd, J_a=2.0 Hz, J_b=4.0 Hz, J_c=13.6 Hz, 1H), 2.57 (dt, J_a=4.0 Hz, J_b=18.4 Hz, 1H), 7.12–7.18 (m, 1H), 7.20–7.28 (m, 4H), 7.57 (dt, J_a=2.4 Hz, J_b=8.8 Hz, 2H), 7.90 (dd, J_a=3.2 Hz, J_b=6.8 Hz, 1H), 8.01 (dd, J_a=2.4 Hz, J_b=3.6 Hz, 1H); ^{13}C NMR: δ=17.0, 29.9, 31.2, 81.5, 121.8, 124.3, 126.0, 126.3, 127.5, 128.8, 131.1, 132.0, 133.0, 133.9, 143.7, 154.5, 179.7, 184.1; IR: ν=3087, 3057, 2985, 2957, 2934, 1680, 1642, 1612, 1595, 1578, 1444, 1383, 1339, 1308, 1263, 1209, 1161, 1103, 1080, 1023, 971, 901, 767, 707, 681, 553 cm^{-1}; HR-MS (ESI): *m/z*=305.3496, calcd. for $C_{20}H_{16}O_3$ [M+H$^+$]: 305.3472.

3,4-Dihydro-2-methyl-2-phenyl-2*H*-naphtho[1,2-*b*]pyran-5,6-dione (10b):[17] Yellow solid, mp 115–117°C, yield: 30% (petroleum ether/ethyl acetate=2/1); ^{1}H NMR ($CDCl_3$): δ=1.66 (s, 3H), 1.95–2.10 (m, 2H), 2.31 (dt, J_a=4.4 Hz, J_b=12.8 Hz, 1H); 2.47 (dt, J_a=4.8 Hz, J_b=16.8 Hz, 1H), 7.12–7.26 (m, 5H), 7.40 (dt, J_a=1.2 Hz, J_b=7.6 Hz, 1H), 7.60 (dt, J_a=1.2 Hz, J_b=7.6 Hz, 1H), 7.91 (ddd, J_a=1.2 Hz, J_b=7.6 Hz, J_c=12.4 Hz, 1H); ^{13}C NMR: δ=16.3, 29.3, 31.9, 82.8, 114.0, 124.0, 126.6, 128.2, 128.7, 128.8, 130.1, 130.9, 132.2, 135.2, 143.6, 161.9, 178.4, 179.5; IR: ν=3063, 2978, 2931, 1689, 1648, 1602, 1489, 1450, 1389, 1307, 1264, 1237, 1156, 1095, 1069, 1031, 993, 966, 913, 767, 701, 668, 560, 538 cm^{-1}.

3,4-Dihydro-2,7-dimethyl-2-phenyl-2*H*,5*H*-pyrano[4,3-*b*]pyran-5-one (10c): Colorless liquid, yield: 55% (petroleum ether/ethyl acetate: 4/1), ^{1}H NMR ($CDCl_3$): δ=1.52 (s, 3H), 1.85–2.02 (m, 2H), 2.11 (s, 3H), 2.25 (dt, J_a=4.0 Hz, J_b=12.4 Hz, 1H), 2.34 (dt, J_a=5.2 Hz, J_b=16.8 Hz, 1H), 5.83 (s, 1H), 7.13–7.19 (m, 3H), 7.20–7.26 (m, 2H); ^{13}C NMR: δ=16.7, 19.8, 29.2, 32.2, 81.2, 98.2, 100.5, 124.2, 127.4, 128.6, 143.7, 160.1, 164.1, 164.9; IR: ν=3085, 3061, 3029, 2979, 2930, 2856, 1707, 1655, 1587, 1495, 1447, 1405, 1380, 1306, 1270, 1240, 1204, 1170, 1133, 1089, 1066, 1035, 995, 952, 910, 884, 849, 811, 765, 738, 702, 535 cm^{-1}; HR-MS (ESI): *m/z*=256.2988, calcd. for $C_{16}H_{16}O_3$ [M]: 256.2964.

1,2,3,5,6,7-Hexahydro-7-methyl-7-phenyl-2-thioxo-4*H*-pyrano[2,3-*d*]pyrimidin-4-one (10d): White solid, mp 202–204°C, yield: 51% (ethyl acetate as eluting solvent), ^{1}H NMR (DMSO-d_6): δ=1.68 (s, 3H), 1.73–1.84 (m, 1H), 1.93–2.14 (m, 1H), 2.21 (dt, J_a=5.2 Hz, J_b=16.4 Hz, 1H), 2.33 (dt, J_a=5.2 Hz, J_b=14.0 Hz, 1H), 7.21–7.29 (m, 1H), 7.31–7.38 (m, 4H), 12.1 (s, 1H), 12.9 (bs, 1H); ^{13}C NMR: δ=15.5, 29.1, 31.4, 83.8, 91.0, 124.6, 127.9, 129.1, 143.7, 156.5, 162.4, 174.0; IR: ν=3142; 3057, 2959, 2901, 2857, 1739, 1633, 1565, 1471, 1442, 1371, 1310, 1262, 1228, 1184, 1132, 1079, 1048, 1009, 905, 882, 846, 759, 725, 696, 676, 608, 567, 535 cm^{-1}; HR-MS (ESI): *m/z*=274.3376, calcd. for $C_{14}H_{14}N_2O_2S$ [M]: 274.3392.

1,5,6,7-Tetrahydro-7-methyl-7-phenyl-2*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*)-dione (10e): White solid, mp 178–180°C, yield: 73% (ethyl acetate as eluting solvent), ^{1}H NMR (DMSO-d_6): δ=1.60 (s, 3H), 1.68–1.82 (m, 1H), 1.91–2.03 (m, 1H), 2.24 (dt, J_a=4.4 Hz, J_b=15.2 Hz, 1H), 2.39 (dt, J_a=5.2 Hz, J_b=13.6 Hz, 1H), 5.18 (s, 1H), 7.26–7.33 (m, 1H), 7.38 (d, J=4.4 Hz, 4H), 10.7 (bs, 1H); ^{13}C NMR: δ=15.6, 29.5, 31.9, 83.1, 85.3, 124.6, 127.7, 129.0, 144.1, 158.5, 165.1; IR: ν=3089, 2978, 2939, 2828, 1732, 1653, 1580, 1529, 1434, 1359, 1312, 1252, 1223, 1163, 1127, 1086, 1061, 1028, 887, 855, 784, 763, 702, 598, 535 cm^{-1}; HR-MS (ESI): m/z=258.2783, calcd. for $C_{14}H_{14}N_2O_3$ [M]: 258.2726.

2,3,4,6-Tetrahydro-2-methyl-6-methyl-2-phenyl-5*H*-Pyrano[3,2-*c*]quinolin-5-one (10f): White solid, mp 143–144°C, yield: 56% (petroleum ether/ethyl acetate=1/2); ^{1}H NMR ($CDCl_3$): δ=1.71 (s, 3H), 2.03–2.15 (m, 1H), 2.23–2.34 (m, 1H), 2.45 (dt, J_a=5.2 Hz, J_b=13.6 Hz, 1H), 2.68 (dt, J_a=5.2 Hz, J_b=17.2 Hz, 1H), 3.67 (s, 3H), 7.19–7.37 (m, 7H), 7.57 (dt, J_a=1.6 Hz, J_b=8.4 Hz, 1H), 8.17 (dd, J_a=2.0 Hz, J_b=8.0 Hz, 1H); ^{13}C NMR: δ=18.1, 29.3, 29.5, 32.4, 80.3, 106.9, 114.0, 116.4, 121.7, 122.6, 124.4, 127.2, 128.6, 130.2, 138.6, 144.5, 155.4, 163.1; IR: ν=3060, 3030, 2976, 2932, 1729, 1635, 1501, 1463, 1416, 1395, 1334, 1319, 1265, 1231, 1192, 1157, 1120, 1092, 1069, 1044, 1030, 974, 916, 840, 756, 701, 587 cm^{-1}; HRMS (ESI): m/z=306.3783, calcd. for $C_{20}H_{19}NO_2$ [M+H$^+$]: 306.3783.

3,4-Dihydro-2-methyl-2-phenyl-2*H*,5*H*-pyrano[3,2-*c*][1]benzopyran-5-one (10g):[4a] White solid, mp 92–94°C, yield: 90% (petroleum ether/ethyl acetate=1/4); ^{1}H NMR ($CDCl_3$): δ=1.73 (s, 3H), 2.08–2.17 (m, 1H), 2.19–2.29 (m, 1H), 2,45 (dt, J_a=4.8 Hz, J_b=13.2 Hz, 1H), 2.60 (dt, J_a=5.2 Hz, J_b=17.2 Hz, 1H), 7.23–7.27 (m, 1H), 7.27–7.36 (m, 6H), 7.51 (td, J_a=1.6 Hz, J_b=8.0 Hz, 1H), 7.97 (dd, J_a=1.6 Hz, J_b=7.6 Hz, 1H); ^{13}C NMR: δ=17.5, 29.3, 32.2, 81.7, 101.1, 115.9, 116.6, 122.3, 123.9, 124.1, 127.6, 128.8, 131.5, 143.7, 152.5, 159.0, 162.9.

Acknowledgements

The authors thank the National Natural Science Fundation of China for the financial support (20903042). The authors are also grateful to Ms. Ping Liang and all the other staffers in the Analytical and Testing Center of HUST, for their supportive and constant contributions to our works. The CNRS and the French Ministry of Research are also strongly acknowledged for their financial support. RDS is grateful to the Agence Nationale de la Recherche (ANR-07-CP2D-07-02) for his PhD grant.

References

[1] a) W. Bannwarth, E. Felder, *Combinatorial Chemistry*, Wiley-VCH, Weinheim, **2000**; b) J. Zhu, H. Bienaymé, *Multicomponent reactions*, Wiley-VCH, Weinheim, **2005**; c) A. Dömling, *Chem. Rev.* **2006**, *106*, 17–89; d) G. Balme, E. Bossharth, N. Monteiro, *Eur. J. Org. Chem.* **2003**, 4101–4111; e) H. Bienaymé, C. Hulme, G. Oddon, P. Schmitt, *Chem. Eur. J.* **2000**, *6*, 3321–3329; f) B. B. Touré, D. G. Hall, *Chem. Rev.* **2009**, DOI: 10.1021/cr800296p.

[2] a) J. D. Sunderhaus, S. F. Martin, *Chem. Eur. J.* **2009**, DOI 10.1002/chem.200802140; b) D. Tejedor, F. Garcia-Tellado, *Chem. Soc. Rev.* **2007**, *36*, 484–491; c) R. V. A. Orru, M. De Greef, *Synthesis* **2003**, 1471–1499; d) V. Nair, C. Rajesh, A. U. Vinod, S. Bindu, A. R. Sreekanth, J. S. Methen, L. Balagopal, *Acc. Chem. Res.* **2003**, *36*, 899–907; e) A. Dömling, I. Ugi, *Angew. Chem.* **2000**, *112*, 3300–3344; *Angew. Chem. Int. Ed.*

2000, *39*, 3168–3210; f) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136.

[3] a) Y. Ohta, S. Oishi, N. Fujii, H. Ohno, *Chem. Commun.* **2008**, 835–837; b) E. R. Bonfield, C. J. Li, *Adv. Synth. Catal.* **2008**, *350*, 370–374; c) A. Zanobini, A. Brandi, A. de Meijere, *Eur. J. Org. Chem.* **2006**, 1251–1255; d) G. M. Mahandru, A. R. L. Skauge, S. K. Chowdhury, K. K. D. Amarasinghe, M. J. Heeg, J. Montgomery, *J. Am. Chem. Soc.* **2003**, *125*, 13481–13485; e) M. Ihara, K. Makita, Y. Tokunaga, K. Fukumoto, *J. Org. Chem.* **1994**, *59*, 6008–6013; f) L. E. Kaim, M. Gizolme, L. Grimaud, *Synlett* **2007**, 227–230; g) D. Basavaiah, D. S. Sharada, A. Veerendhar, *Tetrahedron Lett.* **2004**, *45*, 3081–3083; h) Q. Zhu, H. Jiang, J. Li, M. Zhang, X. Wang, C. Qi, *Tetrahedron* **2009**, *65*, 4604–4613; i) H. Cao, X. Wang, H. Jiang, Q. Zhu, M. Zhang, H. Liu, *Chem. Eur. J.* **2008**, *14*, 11623–11633; j) Y. Ma, M. Wang, D. Li, B. Bekturhun, J. Liu, Q. Liu, *J. Org. Chem.* **2009**, *74*, 3116–3121; k) R. Scheffelaar, N. R. A. Klein, M. Paravidino, M. Lutz, A. L. Spek, A. W. Ehlers, F. J. J. de Kanter, M. B. Groen, R. V. A. Orru, E. Ruijter, *J. Org. Chem.* **2009**, *74*, 660–668; l) N. G. Kozlov, A. P. Kadutskii, *Tetrahedron Lett.* **2008**, *49*, 4560–4562; m) M. Zhang, H. Jiang, H. Liu, Q. Zhu, *Org. Lett.* **2007**, *9*, 4111–4113; n) H. Bradley, G. Fitzpatrick, W. K. Glass, H. Kunz, P. V. Murphy, *Org. Lett.* **2001**, *3*, 2629–2632.

[4] a) G. Appendino, G. Cravotto, L. Toma, R. Annunziata, G. Palmisano, *J. Org. Chem.* **1994**, *59*, 5556–5564; b) V. Nair, P. M. Treesa, C. N. Jayan, N. P. Rath, M. Vairamani, S. Prabhakar, *Tetrahedron* **2001**, *57*, 7711–7717; c) A. Kumar, R. A. Maurya, *Tetrahedron Lett.* **2008**, *49*, 5471–5474; d) A. Kumar, S. Sharma, R. A. Maurya, *Tetrahedron Lett.* **2009**, DOI: 10.1016/j.tetlet.2009.08.046.

[5] L. F. Tietze, N. B. S. Dietz, *Org. Lett.* **2009**, *11*, 2948–2950.

[6] R. Livingstone, D. Miller, S. Morris, *J. Chem. Soc.* **1960**, 3094–3098.

[7] a) R. Andrisano, C. C. Della, M. Tramontini, *Annali di Chimica*, **1967**, *57*, 1073–1086; b) J. Brugidou, H. Christol, *Bull. Soc. Chim. Fr.* **1966**, 2688–2695; c) J. Brugidou, H. Christol, *Compt. Rend.* **1963**, *256*, 3323–3326; d) S. Bilgic, O. Bilgic, B. Buyukkidan, M. Gunduz, *J. Chem. Res.* **2007**, 76–79; e) M. Yalcinkaya, O. Bilgic, S. Bilgic, *Turkish J. Chem.* **1997**, *21*, 215–219; f) B. Buyukkidan, M. Ceylan, *J. Chem. Res. (Syn.)* **2003**, 749–751; g) A. R. Katritzky, X. Lan, *Synthesis* **1992**, 761–764; h) J. Matsumoto, M. Ishizu, R. Kawano, D. Hesaka, T. Shiragami, Y. Hayashi, T. Yamashita, M. Yasuda, *Tetrahedron* **2005**, *61*, 5735–5740.

[8] G. Casiraghi, G. Casnati, A. Pochini, G. Puglia, R. Ungaro, G. Sartori, *Synthesis* **1981**, 143–146.

[9] G. Casiraghi, G. Casnati, G. Puglia, G. Sartori, *Synthesis* **1980**, 124.

[10] D. Boger, S. Weinreb, *Hetero Diels–Alder Methodology in Organic Synthesis* Academic Press, **1987**, p 193ff.

[11] a) S. Cacchi, G. Fabrizi, R. C. Larock, P. Pace, V. Reddy, *Synlett* **1998**, 888–890; b) R. Verhe, N. De Kimpe, D. Courtheyn, L. De Buyck, N. Schamp, *Tetrahedron* **1982**, *38*, 3649–3660; c) W. Hoffmann, *Ger. Offen*. DE 2056196 19720518, **1972**; d) H. M. C. Ferraz, M. K. Sano, M. R. S. Nunes, G. G. Bianco, *J. Org. Chem.* **2002**, *67*, 4122–4126; e) S. Ma, L. Lu, J. Zhang, *J. Am. Chem. Soc.* **2004**, *126*, 9645–9660; f) R. Ballini, S. Gabrielli, A. Palmieri, *Synlett* **2007**, 2430–2432.

[12] a) M. Masuno, T. Asahara, Japanese Patent JP 28002219 19530520, **1953**; b) V. G. Nenajdenko, A. V. Statsuk, E. S. Balenkova, *Tetrahedron* **2000**, *56*, 6549–6556; c) J. A. Vale, D. F. Zanchetta, P. J. S. Moran, J. A. R. Rodrigues, *Synlett* **2009**, 75–78; d) M. Yamauchi, *J. Heterocycl. Chem.* **2002**, *39*, 1013–1018; e) M. Yamauchi, S. Katayama, O. Baba, T. Watanabe, *J. Chem. Soc. Chem. Commun.* **1983**, 281–282.

[13] J. A. Joule, *Science of Synthesis*,Georg Thieme Verlag, Stuttgart, **2001**, Vol. 10, pp 361–652.

[14] a) H. R. Synder, C. W. Smith, J. M. Stewart, *J. Am. Chem. Soc.* **1944**, *66*, 200–204; b) A. V. Novikov, A. Sabahi, A. M. Nyong, J. D. Rainier *Tetrahedron: Asymmetry* **2003**, *14*, 911–915; c) D. T. Jones, G. D. Artman, R. M. Williams *Tetrahedron Lett.* **2007**, *48*, 1291–1294; d) J. S. Yadav, B. V. S. Reddy, A. P. Singh, A. K. Basak, *Tetrahedron Lett.* **2007**, *48*, 4169–4172; e) M. Iwao, O. Motoi, *Tetrahedron Lett.* **1995**, *36*, 5929–5932; f) H. Tanaka, Y. Murakami, S. Torri, *Bull. Chem. Soc. Jpn.* **1989**, *62*, 4061–4062.

[15] a) V. I. Dronov, R. F. Nigmatullina, Y. E. Nikitin, *Zh. Org. Khim.* **1977**, *13*, 1604–1606; b) T. Shimizu, S. Hiranuma, H. Yoshioka, *Jpn. Kokai Tokkyo Koho* JP 88–55862 19880309, **1989**,; c) H. Bohme, E. Mundlos, *Chem. Ber.* **1953**, *86*, 1414–1419.

[16] a) T. Kwak, S. K. Yoo, M. G. Park, *Patent* WO 20008066299, **2008**; b) T. Kwak, I. G. Jo, J. S. Yoon, S. K. Yoo, M. G. Park, *Patent* WO 2008066301, **2008**; c) T. Kwak, S. K. Yoo, M. G. Park, *Patent* WO 2008066297, **2008**; d) S. K. Yoo, M. Park, I. G. Jo, T. Kwak, *Patent* WO 2006088315, **2006**; e) M. Paulino, E. M. Alvareda, P. A. Denis, E. J. Barreiro, G. M. Sperandio da Silva, M. Dubin, C. Gastellu, S. Aguilera, O. Tapia, *Eur. J. Med. Chem.* **2008**, *43*, 2238–2246.

[17] K. Schaffner-Sabba, K. H. Schmidt-Ruppin, W. Wehrli, A. R. Schuerch, J. W. F. Wasley, *J. Med. Chem.* **1984**, *27*, 990–994.

