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ARTICLE *in* ADVANCED SYNTHESIS & CATALYSIS · DECEMBER 2010

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Trimethylchlorosilane and Silicon Tetrachloride in Two Novel Methodologies for the Efficient and Mild Aldol Addition of β-Keto Esters and Malonates to Aldehydes

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Received: July 21, 2010; Published online: December 3, 2010

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201000573.

Abstract: Efficient and mild aldol additions of β-keto esters and malonates to aldehydes are described using two novel protocols in the presence of silicon tetrachloride and trimethylchlorosilane, respectively. Scope and limitations of the methods have been discussed. Moreover the stability of the obtained products, trimethylsilyl protection of the hydroxy group, as well as the role of both silicon tetrachloride and trimethylchlorosilane in attaining the final products have been analyzed.

Keywords: aldol addition; β-keto esters; malonates; silicon tetrachloride; trimethylchlorosilane

Introduction

The aldol addition of readily enolizable 1,3-dicarbonyl compounds, such as β-keto esters and malonates, to aldehydes, is very difficult to achieve even though the products are valuable intermediates in the total synthesis of natural products.[1,2] Standard methodologies failed because of a retro-aldol process or a dehydration reaction to yield the alkylidene compounds. However, the aldol addition of 1,3-dicarbonyl compounds to formaldehyde is a well-establish reaction for hydroxymethylation.[3–7] Aldol addition of metal enolates of malonates has been successfully achieved with α-alkoxy aldehydes in the presence of $ZnCl_2$.[1] Very recently Mahrwald described a catalyst-free aldol addition of several 1,3-dicarbonyl compounds to activated aldehydes like ethyl glyoxylate in good to high yields.[8] Even if this can be considered the most effective procedure ever reported, aromatic aldehydes were completely unreactive while inactivated aliphatic aldehydes were not tested.[8]

In the past years several methods have been tried but even under very mild conditions (i.e., in the presence of weak base or weak acid or in a mixture of both, in proline-organocatalyzed conditions, etc.), variable mixtures of regioisomers, dehydration products and aldol adducts have been observed.[8,9] For example, in the presence of the trimethylsilyl enol ether of 1,3-pentanedione and without any catalysts, benzaldehyde gave the aldol adduct in 40% yield, while other aldehydes failed.[9a] The reaction of *p*-nitrobenzaldehyde with 2-oxocyclopentanecarboxylic acid esters has been reported in the presence of catalytic amounts of KOH or amines to yield complicated mixtures of regioisomeric aldol adducts and condensation products.[9c] Recently, the aldol reaction of 2-oxocyclopentanecarboxylic ester with protected glyceraldehydes in the presence of LDA has been described to give a mixture of diastereomers in low yield.[9f]

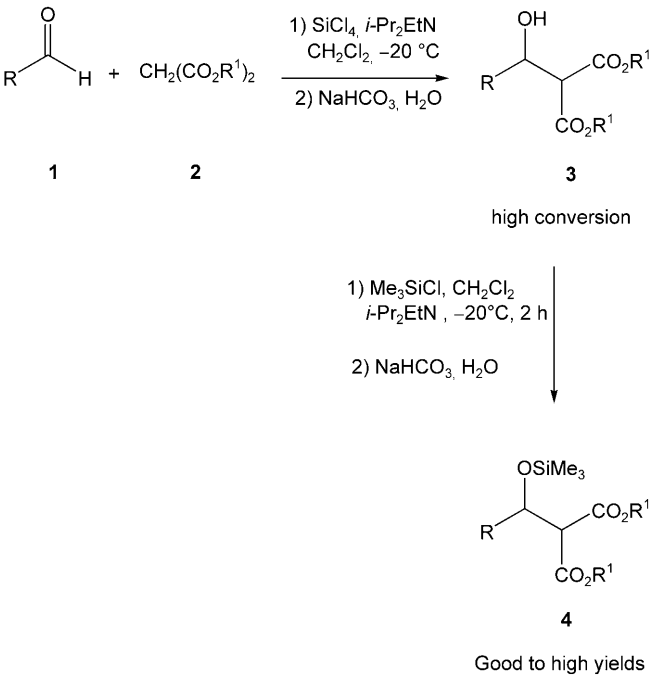
This disappointing situation points out the lack of a general access to these aldol adducts. For that reason, several other synthetic methods have been used to isolate these products.[10–13] The common motif of these methodologies is the *in situ* trapping of the aldol adducts as O-protected compounds. This allows one to avoid both the retro-aldol and dehydration processes. In particular β-keto esters and 2,4-diketones have been successfully used as nucleophiles in the addition to acetals in the presence of Lewis acids to yield protected O-alkyl aldol adducts.[11] Recently Sodeoka reported the first enantioselective addition of β-keto esters to allylic acetals in the presence of

chiral palladium catalyst to give again protected O-alkyl compounds in good yields and *ees*.[12] Chiral O-protected β-hydroxymalonates have been also obtained in diastereoselective oxy-Michael reactions of alkylidene malonates using enantiopure alkoxides.[13]

During our studies about the use of $SiCl_4$ in aldol-type reactions,[14] we found that malonates are efficiently added to a series of representative aromatic, heteroaromatic and unsaturated aldehydes.[15] Even if the resulting β-hydroxymalonates were obtained in quantitative conversion in almost all the cases, they were not stable during the standard purification on silica gel chromatography and even on TLC plates. For this reason a protection reaction performed on the crude product with trimethylchlorosilane was necessary and the aldol adducts were isolated as trimethylsilyl ethers in good to high yields (Scheme 1). In this study it was demonstrated that the concomitant use of both $SiCl_4$ and *i*-Pr_2EtN was necessary, respectively, for the activation of the aldehydes and the *in situ* generation of the active nucleophiles by reversible deprotonation of malonates. It was also established that the trapping of the hydroxy group of the aldol product by $SiCl_4$ as $-OSiCl_3$ species is fundamental to avoid the undesired side-reactions. Finally these species, after aqueous $NaHCO_3$ work-up, afforded the crude free aldol product that was submitted to the protection reaction.

Since the success of this difficult aldol addition is reasonably related to the *in situ* trapping of the aldol adduct, we think that it is possible to obtain directly the trimethylsilyl-protected aldol product in a mild one-pot aldol addition/protection reaction of active methylene compounds with aldehydes in the presence of Me_3SiCl and *i*-Pr_2EtN.

Thus, the development of this idea together with a new application of $SiCl_4$ in the aldol addition of β-keto esters are discussed in the present article.



Scheme 1.

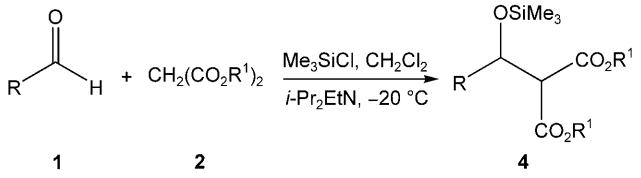
Results and Discussion

One-Pot Aldol Addition of Malonates and β-Keto Esters in the Presence Me_3SiCl and *i*-Pr_2EtN

Preliminary experiments performed on benzaldehyde in the presence of 2 equivalents of trimethylchlorosilane and *i*-Pr_2EtN, emphasized the importance of the *tert*-butyl ester group of malonates in attaining high yields of the protected aldol **4** (Scheme 2, Table 1, entries 1–3). However, no substrate control of the stereoselectivity was detected. When chiral di(−)-menthyl malonate was used a diastereomeric ratio of about 1/1 was observed (Table 1, entry 4).

Control experiments demonstrated that without the concomitant use of both trimethylchlorosilane and *i*-Pr_2EtN, the starting materials were recovered completely unreacted. Different reaction conditions showed a lower reproducibility. Higher reaction temperatures led to variable mixtures of silylated and free aldol adducts. Lower amounts of trimethylchlorosilane ($\leq$1 equivalent) gave no reaction.

Then, in the optimized conditions, we were pleased to observe that all the tested aromatic, heteroaromatic, unsaturated and even enolizable aliphatic aldehydes gave high yields (Scheme 2, Table 2). The results of the enolizable aliphatic aldehydes are particularly interesting because only the new products **4h**



Scheme 2.

Table 1. One-pot aldol addition/protection reaction of malonates with benzaldehyde in the presence of Me_3SiCl and *i*-Pr_2EtN.

Entry	Compound	R^1	Time [h]	Yield of **4** [%][a]
1	**4a**	Me	24	20
2	**4b**	Et	24	51
3	**4c**	*t*-Bu	18	87
4	**4d**	(−)-menthyl	24	52

[a] Yields refer to chromatographically pure compounds

Table 2. One-pot aldol addition/protection reaction of malonates with aldehydes in the presence of Me_3SiCl and *i*-Pr_2EtN.

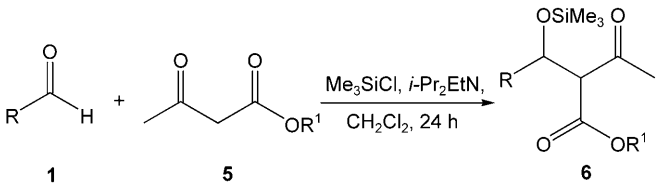
Entry	Compound	R	Time [h]	Yield of **4** [%][a]
1	**4c**	Ph	18	87
2	**4e**	4-$MeOC_6H_4$	18	70
3	**4f**	4-$NO_2C_6H_4$	24	75
4	**4g**	PhCH=CH	24	80
5	**4h**	$PhCH_2CH_2$	5	85
6	**4i**	$CH_3(CH_2)_8$	24	90
7	**4j**	2-furyl	18	90
8	**4k**	4-ClC_6H_4	18	92
9	**4l**	2-ClC_6H_4	24	20

[a] Yields refer to chromatographically pure compounds

and **4i** were obtained, while the dimerization products derived from a possible self-aldol addition were not observed (Table 2, entries 5 and 6).

However, a low yield was obtained with 2-chlorobenzaldehyde (Table 2, entry 9). This result is probably due to the failure of the *in situ* silylation of the aldol adduct rather than the aldol addition itself. Therefore, when the aldol adduct **3l**, easily prepared in quantitative conversion according to Scheme 1, was submitted to the silylation reaction, the product **4l** was similarly obtained in 20% yield, together with the aldehyde and malonate for the retro-aldol reaction.

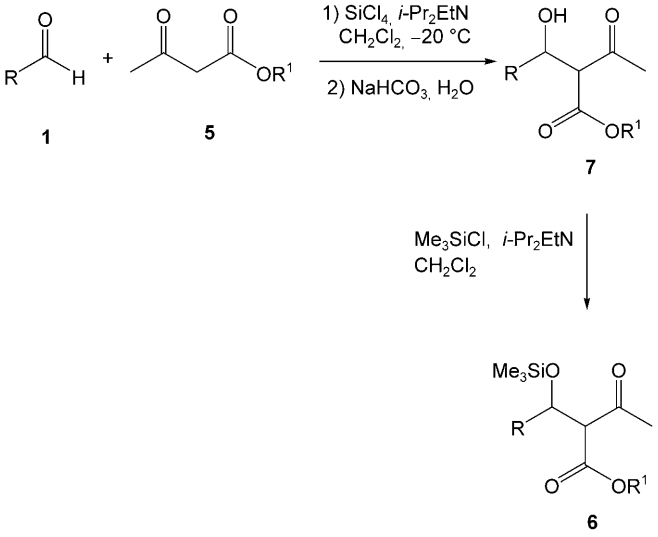
Next, we turned our attention to the reactivity of β-keto esters under similar conditions (Scheme 3, Table 3). Surprisingly, in the presence of *tert*-butyl acetoacetate, benzaldehyde and 3-phenylpropionaldehyde did not react at all (Table 3, entries 1–3), while *p*-nitrobenzaldehyde gave at −20 °C a 1/1 mixture of two inseparable diastereomers in 31% yield (Table 3, entry 4). However, high regioselectivity was detected: the attack of the *p*-nitrobenzaldehyde was observed at the methylene group only. Higher reaction temperature showed no reaction for benzaldehyde and a mixture of starting materials, silylated and free aldol adduct for *p*-nitrobenzaldehyde in similar conversion (Table 3, *cf.* entries 1 and 2 with entries 4 and 5). The reaction of the enantiopure (−)-menthyl acetoacetate led to complex mixture of diastereomers in rather low yield (Table 3, entry 5).



Scheme 3.

Aldol Addition of β-Keto Esters in the Presence of $SiCl_4$ and *i*-Pr_2EtN

The disappointing results of β-keto esters compared to malonates in the one-pot procedure, led us to examine the reactivity of *tert*-butyl acetoacetate in the presence of $SiCl_4$ (Scheme 4, Table 4). In preliminary experiments performed under the same conditions as previously used for the addition of malonates to benzaldehyde (see Scheme 1),[15] *tert*-butyl acetoacetate gave low conversion. A mixture 2/1 of two diastereo-



Scheme 4.

Table 3. One-pot aldol addition/protection reaction of β-keto esters to aldehydes in the presence of Me_3SiCl and *i*-Pr_2EtN.

Entry	Compound	R	R^1	Temperature [°C]	Yield of **6** [%][a]	*dr*[b]
1	**6a**	Ph	*t*-Bu	−20	no reaction	–
2	**6a**	Ph	*t*-Bu	r.t.	no reaction	–
3	**6b**	$PhCH_2CH_2$	*t*-Bu	−20	no reaction	–
4	**6c**	4-$NO_2C_6H_4$	*t*-Bu	−20	31	1/1
5	**6c**	4-$NO_2C_6H_4$	*t*-Bu	r.t.	complex mixture	–
6	**6d**	4-$NO_2C_6H_4$	(−)-menthyl	−20	35	1/2/1

[a] Yields refer to chromatographically pure compounds
[b] Determined by ^1H NMR analysis of crude **6**.

Table 4. Aldol addition of β-keto esters to aldehydes in the presence of $SiCl_4$ and *i*-Pr_2EtN.

Entry	Compound	R	R^1	DMF [equiv.]	M [mol/L]	Yield of **6** [%][a]	*dr*[b]
1	**6a**	Ph	*t*-Bu	0	0.17	20	2/1
2	**6a**	Ph	*t*-Bu	0.4	0.17	31	2/1
3	**6e**	Ph	Me	0.4	0.17	15	2/1
4	**6c**	4-$NO_2C_6H_4$	*t*-Bu	0.4	0.17	41	1.5/1
5	**6a**	Ph	*t*-Bu	0.4	1.0	45	2/1
6	**6c**	4-$NO_2C_6H_4$	*t*-Bu	0.4	1.0	65	1.5/1
7	**6d**	4-$NO_2C_6H_4$	(−)-menthyl	0.4	1.0	30	1/3/1

[a] Yields refer to chromatographically pure compounds
[b] Determined by ^{1}H NMR analysis of the crude aldol **7**.

Table 5. aldol addition of *tert*-butyl acetoacetate to aldehydes in the presence of $SiCl_4$ and *i*-Pr_2EtN.

Entry	Compound	R	Yield of **6** [%][a]	Yield of **8** [%][a,b]	*dr*[c]
1	**6a**	Ph	45	–	2/1
2	**6c**	4-$NO_2C_6H_4$	65	–	1.5/1
3	**6f**	4-CNC_6H_4	48	5	1.5/1
4	**7g**	2-CNC_6H_4	26[e]	–	1.3/1
5	**6h**	4-ClC_6H_4	38	9	1.5/1
6	**6i**	2-furyl	decomp.	39[d]	1.5/1
7	**6j**	PhCH=CH	decomp.	–	–
8	**6k**	4-$MeOC_6H_4$	decomp.	–	–
9	**6b**	$PhCH_2CH_2$	no reaction	–	–

[a] Yields refer to chromatographically pure compounds
[b] Elimination products.
[c] Evaluated by ^{1}H NMR analysis of the crude aldol **7**.
[d] *tert*-Butyl (2-furfurylidene)acetoacetate was characterized according to Ref.[18]
[e] Yield refers to product **7g**.

mers was observed, even if with high regioselectivity, for the attack at the methylene group. As observed before for compounds **3** in the aldol addition of malonates (Scheme 1),[15] attempts at purification of crude product **7** led to decomposition of the aldol adduct and only the starting materials were isolated. Therefore the protection of the hydroxy group with trimethylchlorosilane was necessary but **6** was still isolated in low yield (Table 4, entry 1). Better results were observed when dimethylformamide (DMF) was used for the activation of $SiCl_4$ (Table 4, entry 2).[16] Under these conditions, the *tert*-butyl ester was the most effective while methyl acetoacetate was still poorly reactive (Table 4, entry 3). However, in the presence of *p*-nitrobenzaldehyde we observed higher conversion for **7** and **6** was isolated in 41% yield (Table 4 entry 4), pointing out that this aldehyde can be considered a better model substrate.

A further improvement was observed for both benzaldehyde and *p*-nitrobenzaldehyde when the concentration of the reaction medium increased from 0.17 M to 1.0 M (Table 4, entries 5–7). In particular, performing the reaction in the presence of the commercially available 1 M dichloromethane solution of $SiCl_4$ only, we were pleased to observe that *p*-nitrobenzaldehyde gave almost a quantitative conversion even if with rather low diastereoselectivity (Table 4, entry 6). Then, after the treatment with TMSCl, **6** was isolated with a very interesting 65% yield for the two consecutive steps.

Enantiopure (−)-menthyl acetoacetate was not reactive in the presence of benzaldehyde, while with *p*-nitrobenzaldehyde it gave a complex mixture of diastereomers in a rather low yield (Table 4, entry 7). Control experiments performed in the presence of only $SiCl_4$ led to complex mixtures of products and *i*-Pr_2EtN alone was not able to promote the reaction.

Then, in the optimized conditions the scope and the limitations of the method were analyzed in the presence of *tert*-butyl acetoacetate (Table 5). In the case of 2-furfural and aromatic aldehydes bearing, respectively, a *p*-cyano, *o*-cyano, *p*-chloro group, ^{1}H NMR analysis of the crude mixtures revealed very good conversions for the aldol **7**, but with rather low diastereoselectivity (Table 5, entries 3–6), However TMS-protections gave variable results because of the low stability of the aldol adducts **7** shown even under the used mild conditions. In particular, α,β-unsaturated compounds **8** were isolated after the TMSCl treatment of crude aldol **7f** and **7h** because of the elimina-

tion reaction. In this way **6f** and **6h** were obtained in yields comparable to that of benzaldehyde (Table 5, entry 3). Moreover in the attempt at silylation of aldol **7i** only the elimination product and the starting materials were isolated (Table 5, entry 6). As observed before (Table 2, entry 9), in the presence of a cyano group in the *ortho* position, we were not able to isolate the protected aldol **6g** (Table 5, entry 4). The chromatography of the crude mixture, gave us the possibility to isolate a free aldol adduct **7g** even if in low yield (Table 5, entry 4).[17] In this case the starting materials were also isolated because of a retro-aldol reaction occurring during the chromatography.

On the other hand attempts at aldol additions to cinnamaldehyde and *p*-methoxybenzaldehyde led to complex mixtures of products (Table 5, entries 7 and 8) and we did not perform the trimethylsilyl protection. Moreover, as usually reported for aliphatic aldehydes in other $SiCl_4$-mediated transformations,[14,15,16] 3-phenylpropionaldehyde did not react at all.

The pathway of the aldol addition of β-keto esters to aldehydes in the presence of $SiCl_4$ and *i*-Pr_2EtN can be considered as being similar to the addition of malonates, whose mechanism was previously discussed in the introduction section.[15]

The two novel $SiCl_4$- and Me_3SiCl-based methodologies show several common features. In particular, in both the cases, the *in situ* formation of the active nucleophilic species can be attributed to *i*-Pr_2EtN for the reversible deprotonation of the methylene active compounds. Moreover both $SiCl_4$ and Me_3SiCl led to protected aldol adducts, a requisite to avoid the undesired retro-aldol and elimination reactions. In the case of $SiCl_4$, the final aldol adducts are reasonably obtained as $-OSiCl_3$-protected compounds. As reported in the literature, the $-OSiCl_3$ group is not stable and it can be hydrolyzed under the mild work-up conditions to afford the unprotected hydroxy derivatives.[14b,15,16]

However, the role of Me_3SiCl in the one-pot reaction is not fully clarified at the present. We presume that Me_3SiCl can also activate the carbonyl group as a Lewis acid.[19] As another possibility, intermediate formation of silyl enol ethers and silyl ketene acetals is expected. In fact these species are reported to form from simple ketones and esters under not very different reaction conditions.[20]

Conclusions

In this article we have described two efficient protocols for the aldol addition of β-keto esters and malonates to aldehydes based on the use of Me_3SiCl and $SiCl_4$, respectively. In particular, in the presence of Me_3SiCl and *i*-Pr_2EtN, aromatic, heteroaromatic, unsaturated and even enolizable aliphatic aldehydes reacted with malonates in high yields to afford directly the silyl-protected aldol adducts. However, this one-pot procedure was less effective for β-keto esters.

On the other hand, $SiCl_4$ was very effective for the aldol addition of both β-keto esters and malonates. The resulting free aldol adducts were obtained in good to high conversions. These compounds showed low stability during chromatography. For that reason the trimethylsilyl protection of the hydroxy group performed on the crude aldols was necessary for the isolation and the characterization of the final products.

Since comparable methods to access of aldol adducts of malonates and β-keto esters have never been reported before for this wide range of aldehydes, further studies are currently under way to expand the scope with respect to both the electrophile and active methylene components and to develop asymmetric versions of the reactions.

Experimental Section

General Remarks

All reactions were performed in oven-dried (140 °C) or flame-dried glassware under dry N_2. Dichloromethane was reagent grade and was dried and distilled immediately from CaH_2 before use. Column chromatographic purification of products was carried out using silica gel 60 (70–230 mesh, Merck). The reagents (Aldrich and Fluka) were used without further purification. The NMR spectra were recorded on Bruker DRX 400, 300, 250 spectrometers (400 MHz, 300 MHz, 250 MHz for ^1H; 100 MHz, 75 MHz, 62.5 MHz for ^{13}C). Spectra were referenced to residual $CHCl_3$ (7.26 ppm, ^1H, 77.23 ppm, ^{13}C). Coupling constants *J* are reported in Hz. Yields are given for isolated products showing one spot on a TLC plate and no impurities detectable in the NMR spectrum. Mass spectral analyses were carried out using an electrospray spectrometer, Waters 4 micro quadrupole. Elemental analyses were performed with FLASHEA 1112 series-Thermo Scientific for CHNS-O apparatus.

General Procedure for One-Pot Aldol Addition–Silylation Reaction in the Presence of Me_3SiCl and *i*-Pr_2EtN

In a flame-dried, 2-necked, round-bottom flask, aldehyde (0.40 mmol) was added to a solution of *i*-Pr_2EtN (2.0 equiv., 0.80 mmol), malonate diester (1.1 equiv., 0.44 mmol) and Me_3SiCl (2.0 equiv., 0.80 mmol) in dry dichloromethane (2.0 mL) under nitrogen at −20 °C. At the end of the reaction, the mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL), extracted with 15×3 mL of CH_2Cl_2 and dried over anhydrous Na_2SO_4. After removing the solvent under reduced pressure, the crude oil was purified by flash chromatography from hexane to 95/5 hexane/AcOEt mixture to afford the pure products **4**.

General Procedure for $SiCl_4$-Mediated Aldol Reaction

In a flame-dried, 2-necked, round-bottom flask, acetoacetate esters (1.5 equiv., 0.60 mmol) was added to a solution of *i*-Pr_2EtN (2.0 equiv., 0.80 mmol), $SiCl_4$ (1.1 equiv., 0.44 mL of 1.0 M solution in CH_2Cl_2), DMF (0.10 mmol) and aldehyde (0.40 mmol) under nitrogen at −20 °C. At the end of the reaction, the mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL), extracted with 15×3 mL of CH_2Cl_2 and dried over anhydrous Na_2SO_4. After removing the solvent under reduced pressure, the crude products **7** were analyzed by ^1H NMR and submitted to TMS protection.

General Procedure for Trimethyl Silyl Protection of Crude Aldols 7

Diisopropylethylamine (2.0 equiv., 0.8 mmol) and trimethylsilyl chloride (2.0 equiv., 0.8 mmol) were added to a solution of the crude product **3** in dry dichloromethane (3.0 mL) at −20 °C under nitrogen. At the end of the reaction, the mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL), extracted with 15×3 mL of CH_2Cl_2 and dried over anhydrous Na_2SO_4. After removing the solvent under reduced pressure, the crude oil was purified by flash chromatography from hexane to 95/5 hexane/AcOEt mixture to afford the pure products **6**.

All the compounds **6** are new. For their spectroscopic data see supporting information.

Supporting Information

Spectroscopic data of the new compounds **4d**, **4g**, **4h** and **6** are reported in the Supporting Information. For all the other compounds see Ref.[15]

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