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Efficient Acetalisation of Aldehydes Catalyzed by Titanium Tetrachloride in a Basic Medium

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Abstract: The acetalisation of aliphatic and aromatic aldehydes is achieved in a basic medium by using catalytic amount of Ti(IV) chloride in MeOH in the presence of NH_3 or Et_3N. The present protocol shows many advantages over the well known base or acid catalysis: in fact, in contrast to base-promoted acetalisation, aldehydes with electron-rich carbonyl groups react easily, enolizable aldehydes do not undergo aldol condensation and, in contrast to acid-catalysis, migration of the double bond does not occur in the preparation of α,β-unsaturated acetals.

Introduction

Acetalisation is usually employed in organic synthesis for the protection of aldehydes and ketones. The acid-catalysis is the common feature linking all of the methods of acetal formation,[1] however the reaction is reversible and, in most cases, it is necessary to shift the equilibrium to the side of the products.

Although acetals are easily hydrolysed by acids, they possess virtually unlimited stability to basic conditions but very few methods have been reported for acetalisation in basic media,[1a] and all of them are limited to aldehydes or ketones with a very electron-deficient carbonyl group[2] and/or without an α-hydrogen atom[2a] (aldol condensation takes over during acetalisation in basic medium).

Recently, several Lewis acids[1d-h] have been reported to offer major advantages over general Bronsted acid catalysis, but the search for new catalysts to generate acetals under mild conditions is still actively pursued.

We report herein a mild and facile approach to a large variety of acetals which is based on the catalytic use of Ti(IV) chloride (1 mol %) in a basic medium according to eq 1.

$$\mathrm{RCHO} \xrightarrow[\mathrm{MeOH\ /\ NH_3\ or\ Et_3N}]{\mathrm{TiCl_4\ (1\ mol\%),\ 0.5\ h,\ 0^\circ C}} \mathrm{RCH(OMe)_2} \qquad (1)$$

To the best of our knowledge, this is the first example in which a Lewis acid catalyses acetal formation under basic conditions.

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Results

Two series of experiments were carried out. In the first (method A) acetalisation was accomplished by bubbling ammonia gas into a methanolic solution (10 mL) of the aldehyde (5 mmol), to which a catalytic amount of $TiCl_4$ was previously added, until pH ≅ 8-9 was achieved. The reaction proceeded smoothly at 0°C and was complete within half an hour, and either anhydrous or commercial HPLC grade methanol gave the same acetal yields.

In the second series (method B) the reactions were repeated, under comparable experimental conditions, using triethylamine (Et_3N, 0.6 mmol) instead of ammonia. The results obtained with both methods are listed in Table.

By using the appropriate catalyst concentration (see later), aliphatic, α,β-unsaturated and aromatic aldehydes readily gave good to excellent yield of acetals. The crude acetals recovered after work up mostly showed an NMR purity (conversion) ≥ 96%. In these cases the isolated yield of products, reported in Table, refer to the crude acetals without further purification. Partial decomposition of the acetal into the starting aldehyde may occur during purification by silica gel column chromatography.

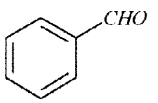
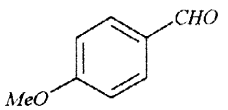
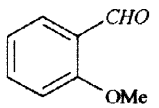
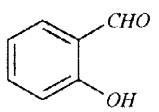
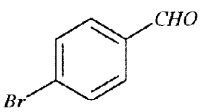
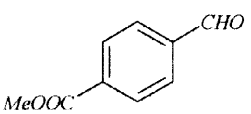
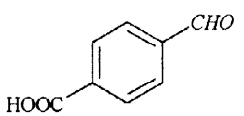
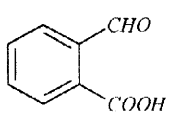
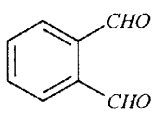
This investigation had a double purpose. One was to explore whether the properties of the added base might influence the catalyst activity; the other more specific aim was to draw some information on the probable mechanism involved.

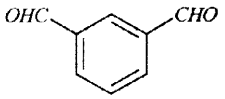
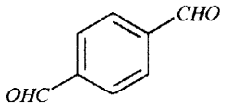
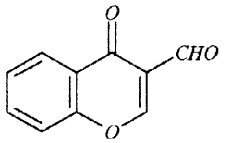
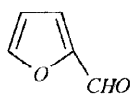
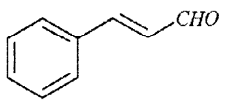
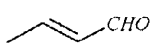
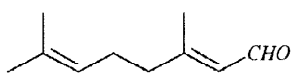
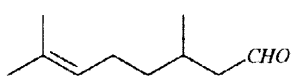
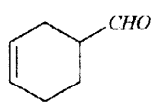
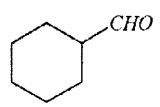
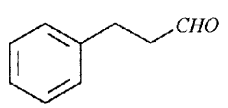
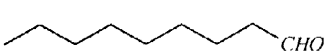
The major difference between the two methods is that 1 mol% of $TiCl_4$ was uniformly efficient with Et_3N for all the twenty four aldehydes investigated (a standard $TiCl_4$/ Et_3N /RCHO ratio of 1:12:100 was inavariably used). On the contrary, the amount of catalyst required to give a clean high-yielding acetalisation with ammonia was strongly dependent on the nature of the aldehyde.

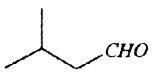
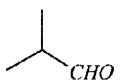
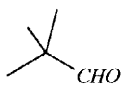
Thus, whereas 1 mol % of $TiCl_4$ was sufficient with aromatic and α,β-unsaturated aldehydes, a higher concentration of $TiCl_4$ was needed to obtain good yields of acetals with aliphatic aldehydes (entries r, s, t, u', v, w, y, z).

Aliphatic aldehydes in the presence of 1 mol % of catalyst underwent competitive formation of "aldehyde-ammonia" addition products (eqs 2 and 3) with dramatic decrease of acetal yield (entry u, comparable results were obtained with other aliphatic aldehydes). Notably, the catalytic process performed on a laboratory scale with Et_3N by using two model systems (*p*-bromobenzaldehyde and 3-phenylpropionaldehyde, 50 mmol) worked well even with 0.1 mol % of $TiCl_4$ without decreasing the yields (entries e''' and u''''). When the reaction was performed in a small scale (5 mmol of RCHO) it was too difficult to measure 5 μL of the 1.0 M $TiCl_4$ solution (0.1 mol%).

Table. $TiCl_4$ Catalyzed Acetalization of Aldehydes in $MeOH/NH_3$ (Method A) and $MeOH/Et_3N$ (Method B)

Entry	Aldehyde	Acetal	Method $TiCl_4/RCHO$[a]	Yields of Acetals conversion(%)[b]	isolated yield (%)[c]
a		**1**	A	98	96
a'			B	94	90[d]
b		**2**	A	85	79[d]
b'			B	81	
c		**3**	A	98	94
c'			B	90	
d		**4**	B	74	68[f]
e			A	95	
e'		**5**	A(1:1000)	93	90[e]
e''			B	98	95
e'''			B(1:1000)	98	96
f		**6**	B	80	70[f]
g		**7**	B	99	92
h		**8**[g]	B	94	88[f]
i		**9**[h]+**10**[i]	B	57+36	52+30[f]

j		**11**[i]	B	96	93
l		**12**[i]	B	94	90
m		**13**[k]	B	98	94
n		**14**	A	98	94
n'			B	98	95
o		**15**	A	99	98
o'			B	90	
p		**16**	A	98[l]	95
p'			B	>99[l]	95
q		**17**	B	84	79[d]
r		**18**	A(1:6)	98	96
r'			B	92	
s		**19**	A(1:6)	97	91
s'			B	70	
t		**20**	A(1:6)	>99	98
t'			B	98	96
u			A	50[m]	
u'			A(1:6)	96	93
u"		**21**	A(1:1000)	traces[n]	
u"'			B	96	94
u""			B(1:1000)	95	90[d]
v		**22**	A(1:6)	>99[l]	95
v'			B	90[l]	

w		**23**	A(1:6)	>99[l]	96
w'			B	89[l]	
y		**24**	A(1:6)	>99[l]	97
y'			B	88[l]	
z		**25**	A(1:6)	97[l]	95
z'			B	74[l]	

[a]If not otherwise stated the $TiCl_4$:RCHO ratio was 1:100. [b]The conversion was determined by ^1H NMR spectroscopy analysis of the crude reaction mixture (the reminder to 100% was the starting aldehyde). [c]When the purity of the crude acetal by ^1H NMR spectroscopy was ≥ 96%, isolated yields (%) refer to the recovered crude acetal without further purification. [d]Purified by Kugelrohr distillation. [e]On standing at room temperature the unreacted aldehyde crystallized out from the crude reaction mixture and, upon filtration of the solid, the acetal was obtained. [f]Purified by flash column chromatography (hexane/Et_2O/$CHCl_3$, 8:1:1). [g]**8** is 3-methoxy-3H-isobenzofuran-1-one. [h]**9** is 1,3-dimethoxy-1,3-dihydro-isobenzofuran. [i]**10**, **11** and **12** are the respective tetramethylacetals. [k]Selective acetalisation of the aldehydic function occurred. [l]To determine the conversion of volatile aldehydes, the reaction mixture was extracted with CCl_4 and the organic layer, without further concentration, was treated with an internal standard and analyzed by ^1H NMR spectroscopy. [m]46% of 2,4,6-triphenethylhexahydrotriazine was also formed. [n]Triazine was the main product.

Parallel experiments performed with ammonia showed that *p*-bromobenzaldehyde still reacted cleanly (entry e') but 3-phenylpropionaldehyde gave mainly 2,4,6-triphenethylhexahydrotriazine (eq 3, entry u"). However, by using the appropriate concentration of catalyst, method A appears to be quite general for aliphatic, α,β-unsaturated and aromatic aldehydes, as well as method B.

The present procedures, in addition to their wide applicability and ready feasibility, offer some useful advantages over the known acid or base catalysis: 1) in contrast to acetalisation in basic media[1a,2], aldehydes with electron rich carbonyl groups reacted easily and enolizable aldehydes did not undergo aldol condensation; 2) in contrast to acid-catalysis, migration of the double bond did not occur, and aromatic bromide, furan and ester groups were inert also.

This protocol is far superior, with respect to both methodology and applicability, to the recently reported procedure[3] in which acetalization was achieved by reacting an aldehyde with equimolar amount of $Ti(OR)_4$ and 5 mol % of $TiCl_4$ in abs. hexane. Under these conditions α,β-unsaturated aldehydes did not react and dimethyl acetals could not be obtained, owing to the low solubility of $Ti(OMe)_4$.

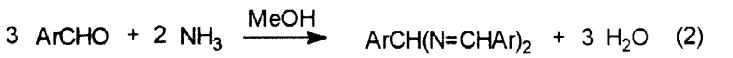
Among the aldehydes investigated, only 2-carboxybenzaldehyde and phthalaldehyde failed to produce the desired acetals giving 3-methoxy-3H-isobenzofuran-1-one **8** (entry h) and 1,3-dihydro-isobenzofuran **9** (entry i) as the main product, respectively. Both carbonyl groups of phthalaldehyde, isophthalaldehyde and terephthalaldehyde were acetalised (entries i-l) but, interestingly, 3-formylchromone underwent selective acetalisation at the aldehydic function (entry m). Preliminary experiments showed that this catalyst system is not effective on aromatic and acyclic ketones according to the chemoselectivity observed for 3-formylchromone.

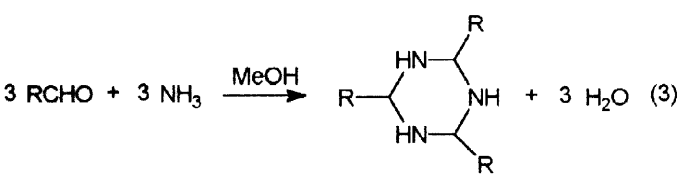
Discussion

Under acid-catalysis,[4] electron-withdrawing substituents α to the carbonyl enhance and electron-donating groups (such as phenyl or conjugation) hinder acetal formation. In basic media, [1a,2] only aldehydes with strongly electron deficient carbonyl groups can undergo acetalisation.

In sharp contrast with this effect of substituents, our results clearly show up that aromatic and α,β-unsaturated are more reactive than aliphatic aldehydes under condition of method A, where ammonia addition to the carbonyl carbon may compete with acetal formation.

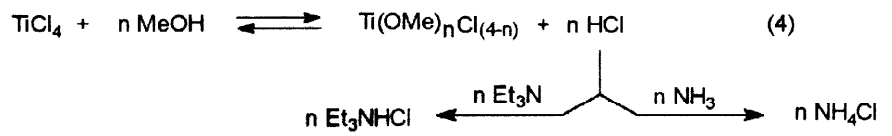
In fact, aldehydes easily react with ammonia in methanol,[5] according to eq 2 (aromatic and α,β-unsaturated) or to eq 3 (aliphatic), to give hydrobenzamides or trimers.





We have found that the amount of $TiCl_4$ required to overcome these competitive reactions is much higher for aliphatic than for aromatic and α,β-unsaturated aldehydes (ratio RCHO/$TiCl_4$, 6:1 and 1000:1, respectively).

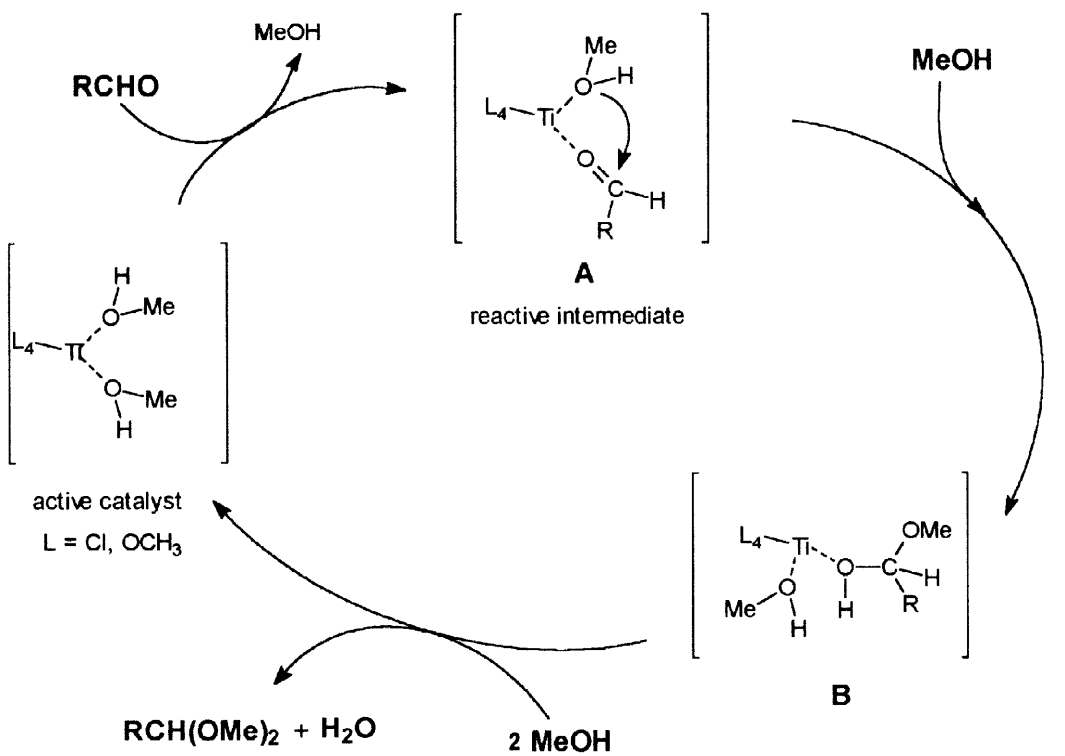
The catalyst of the present reaction is neither $TiCl_4$ nor $Ti(OCH_3)_4$. We proved that $TiCl_4$ in methanol does not promote any acetal formation even after many hours,[6] and that $Ti(OCH_3)_4$ is highly insoluble in MeOH.[3,9] Very likely, the active catalyst is a chlorotitanium methoxide $Ti(OCH_3)_nCl_{4-n}$, generated *in situ* by adding the base (NH_3 or Et_3N) to the methanolic solution of $TiCl_4$ (eq 4).



The base, which merely acts as an acid quencher, shifts the equilibrium of reaction of eq 4 to the right increasing the concentration of the active catalyst.[10]

To account for the "inverse" effect of substituents, we postulate a catalytic cycle (Scheme) focused on the formation of a reactive intermediate of type **A**,[11] in which the six-coordinative valence of $Ti(OCH_3)_nCl_{4-n}$ (TiL_4 in Scheme) is saturated by MeOH and RCHO. Thus, the catalytic activity can be attributed to the Lewis acidity of the metal and to its ability to act as a template for the simultaneous activation of MeOH and RCHO.

Scheme



As a consequence, methanol addition to the carbonyl carbon is a very fast "*quasi* intramolecular" concerted reaction. Transfer of methanol from the metal to the aldehyde frees up a coordinative site, subsequently filled with another methanol to produce adduct **B**. Further conversion

of the complexed hemiacetal **B** into the acetal very probably proceeds *via* prior formation of an oxocarbenium ion (S_N1),[12] which subsequently undergoes external addition of MeOH.

This catalytic cycle is efficient, provided that the ligand exchange occurs at a fast enough rate to keep the equilibrium concentration of **A** high enough to prevent any competitive intermolecular reactions involving the aldehyde (ammonia addition and/or aldol condensation). In fact, formation of **A** and its regeneration implies that the aldehyde must firstly displace the excess of MeOH from the coordination sphere of the metal and, then, the water[13] and the product will be formed.

An electron-donor substituent R in the aldehyde, by strengthening the bond that the carbonyl oxygen forms with the metal, helps to stabilise adduct **A** and favours a faster replacement of the weakly coordinated ligands.[14]

With the less basic aliphatic aldehydes, the ligand exchange is slower and the amount of $TiCl_4$ must be increased in order to compensate for the low reaction rate and to overcome the faster addition of ammonia. Under the present conditions, the overall effect of substituents is thus strengthened because both the rate of formation of **A** and of the reaction involving cation formation from **B** would change corresponding to different substituents in precisely the same way.

Conclusions

In conclusion we have reported a very simple, yet very efficient methodology for acetalisation of aldehydes, which represents a valid supplement to the existing procedures. We hope this new protocol will be of general utility to synthetic organic chemists for the protection of aldehydes bearing acid-sensitive functional groups. Further studies are in progress in our laboratory with the aim of better evaluating the selectivity of acetalisation among differently substituted carbonyl groups.

Experimental Section

General Remarks. $TiCl_4$ (1.0 M solution in CH_2Cl_2) and methanol ACS (HPLC grade) were purchased from Aldrich and used as received. Et_3N and liquid aldehydes were distilled prior to use. 4-Carboxybenzaldehyde and solid aldehydes were used as received. All reactions were carried out at 0°C under a nitrogen atmosphere. ^1H NMR spectra were recorded in $CDCl_3$ solution on a Bruker AC-250 MHz instrument with Me_4Si as an internal standard. To determine the conversion with the more volatile aldehydes (see Table), the crude reaction mixture was extracted with CCl_4 and the organic layer, after the addition of an internal standard, was directly analyzed by ^1H NMR spectroscopy without further concentration. Mass spectra were taken on Finnigan MAT-TSQ70

spectrometer. Melting points were taken on a Kofler apparatus (uncorrected). Flash column chromatography was performed using Merck silica gel 60 (particle size 0.004-0.063). Microanalyses were performed by the Analytical Section of REDOX Laboratories, Cologno Monzese (MI).

General Procedure for the $TiCl_4/NH_3$ Catalyzed Acetalisation of Aromatic and α,β-Unsaturated Aldehydes (Method A). 5 mmol of freshly distilled aldehyde was dissolved in 10 mL of MeOH. To the well stirred methanolic solution of the aldehyde, kept at 0°C under N_2, was added with a syringe, in one portion, 50 μL (5 x 10^{-2} mmol) of a 1.0 M $TiCl_4$ solution in CH_2Cl_2. After *ca.* 15 min ammonia gas was bubbled into the solution at 0°C. The bubbling was stopped when NH_4Cl started to precipitate, as a white solid, from the solution (pH ≈ 8-9). The heterogeneous mixture was stirred at room temperature for an additional 15 min. Water (2 mL) was then added and the clear solution was extracted with Et_2O (3 x 30 mL). The organic layers were collected , washed with water (2 x 5 mL), dried over Na_2SO_4 and evaporated under reduced pressure. When the crude residue (generally, an oil) showed an ^1H NMR purity ≥ 96%, no further purification was undertaken, and the isolated products yields (%) in Table refer to the weight of the recovered crude acetals. Yields based on the converted aldehydes were always quantitative. When the ^1H NMR purity was ≤ 95%, the crude residue was purified by flash column chromatography or by Kugelrohr distillation.

General Procedure for the $TiCl_4/NH_3$ Catalyzed Acetalisation of Aliphatic Aldehydes (Method A). To prevent the competitive formation of "aldehyde-ammonia" addition products, it was necessary to add a larger amount of $TiCl_4$ (0.84 mmol, 0.84 mL of the 1.0 M solution) to the methanolic solution (10 mL) of the aliphatic aldehydes (5 mmol). The other experimental conditions and work up were the same as in the preceding procedure.

General Procedure for the $TiCl_4$/ Et_3N Catalyzed Acetalisation of Aliphatic, Aromatic and α,β-Unsaturated Aldehydes (Method B). 5 mmol of freshly distilled aldehyde was dissolved in 10 mL of MeOH. To the well stirred methanolic solution of the aldehyde, kept at 0°C under N_2, was added with a syringe, in one portion, 50 μL (5 x 10^{-2} mmol) of a 1.0 M $TiCl_4$ solution in CH_2Cl_2 and, after 15 min, 83 μL (0.6 mmol) of Et_3N. Upon addition of Et_3N, formation of a precipitate (Et_3NHCl) was not observed. The reaction mixture was, then, stirred at room temperature for an additional 15 min. Further work up was similar to that of method A.

Spectroscopic Data. With the exception of 4-dimethoxymethylbenzoic acid 7, all the products listed in Table are known compounds and their spectroscopic and analytical data are identical to those reported in the literature.[15] We include spectroscopic data of the newly prepared acetal 7 and of acetals **4**, **6**, and **23** because they are incomplete in the literature.

Salicylaldehyde dimethyl acetal (4). Colourless liquid, $bp_{0.01}$ 64°C,[16] ^{1}H NMR ($CDCl_3$) δ 3.38 (6H, 2 OCH_3, s), 5.55 (1H, C<u>H</u>-$(OCH_3)_2$, s), 6.88 (2H, Ar H, m), 7.20 (2H, Ar H, m), 8.08 (1H, OH, s, D_2O exchangeable), MS *m/z* 168 (M^+, 10), 137 (M-OCH_3, 15), 136 (M-CH_3OH, 17), 121 (20), 107 (20), 32 (100); IR ν_{max} 3372, 1365, 1247-1050 cm^{-1}.

4-Dimethoxymethylbenzoic acid methylester (6). White solid, recrystallized from light petroleum; mp 30 °C (lit.[17] 32-3 °C); ^{1}H NMR ($CDCl_3$) δ 3.31 (6H, 2 OCH_3, s), 3.93 (3H, $COOCH_3$, s), 5.45 (1H, C<u>H</u>-$(OCH_3)_2$, s), 7,52 (2H, Ar H, d, J=9 Hz), 8.04 (2H, Ar H, d, J=9 Hz); MS *m/z* 210 (M^+, 8), 179 (M-OCH_3, 100), 148 (2), 133 (8), 120 (8), 105 (9), 91 (9), 77 (9), 75 (12); IR ν_{max} 1727, 1280, 1103-987 cm^{-1}.

4-Dimethoxymethylbenzoic acid (7). White solid recrystallized from Et_2O; mp 118-9 °C; ^{1}H NMR ($CDCl_3$) δ 3.35 (6H, 2 OCH_3, s), 5.47 (1H, C<u>H</u>-$(OCH_3)_2$, s), 7,52 (2H, Ar H, d, J=8.55 Hz), 8.12 (2H, Ar H, d, J=8.55 Hz); MS *m/z* 197 (M+1, 5), 195 (M-1, 6), 179 (M-OH, 6), 165 (M-OCH_3, 100), 149 (8), 120 (5), 91 (8), 77 (9); IR ν_{max} 3434, 1685, 1103-1053 cm^{-1}. Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.12; O, 32.65. Found: C, 61,17; H, 6.16.

Isovaleraldehyde dimethyl acetal (23). Colourless liquid, bp 132-3 °C,[18] ^{1}H NMR ($CDCl_3$) δ 0.90 (6H, $2CH_3$, d, J=6.5 Hz), 1.40 (2H, CH_2, t, J=6.5 Hz), 1.68 (1H, C<u>H</u>-$(CH_3)_2$, m), 3.20 (6H, 2 OCH_3, s), 4.32 (1H, C<u>H</u>-$(OCH_3)_2$, t, J=6.5 Hz).

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References and Notes

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