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COMMUNICATION

$FeCl_3.6H_2O$/acetaldehyde, a versatile system for the deprotection of ketals and acetals *via* a transacetalization process

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Mild and efficient catalytic deprotection of ketals/acetals mediated by $FeCl_3.6H_2O$/acetaldehyde has been described in this paper. The versatility and high chemoselectivity of the iron(III)/aldehyde system is demonstrated by a large scope of examples. Deprotected ketones/aldehydes are nearly quantitatively isolated after a filtration over a pad of silica gel followed by evaporation of volatile by-products.

The Wieland-Miescher Ketone (WMK) and derivatives such as **1** (figure 1) are particularly useful synthons for the construction of a variety of biologically active compounds belonging to terpenoids and steroids family.[1, 2, 3]

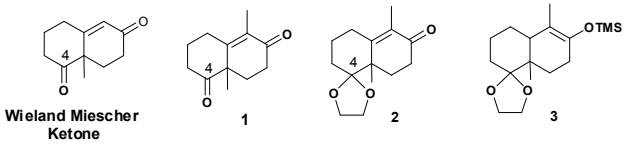

Figure 1 : Wieland Miescher Ketone and derivatives **1**, **2** and **3**.

The rigid bicyclic structure with functionalities in both cycles and the availability of the starting WMK in the enantiopure form makes the latter compound an outstanding synthon for total synthesis of terpenoids.[2a,2d,4] Furthermore, the two ketone functions do not present the same reactivity and can be chemically differentiated by selective reduction or protection as dioxolane **2**[4] of the more electrophilic unconjugated one (C-4). Ketals and acetals such as dioxolane group occupy a centered position for the protection of ketones and aldehydes due to their rather good stability towards nucleophilic and basic reagents.[5] Considerable efforts have been directed towards developing mild and selective methods for ketals/acetals deprotection.[6] However, search for efficiency and chemoselectivity for this purpose is always useful.

For example, the presence of a quaternary centre adjacent to the dioxolane moiety of compounds resulting from chemical transformations of **2** or **3** may sometimes cause difficult or uncompleted ketal hydrolysis and subsequently a tricky separation step. Thus, in 1999, Marko *et al.* described a nearly quantitative deprotection (91% yield) of the dioxolane part of the protected ketone type Wieland-Miescher using Cerium Ammonium Nitrate (CAN) in excess in a biphasic system CH_3CN/H_2O.[7,8] Some other more classical acidic conditions (HCl 1 to 12M in MeOH[9] or 3N to 4N in THF[10,2d]) were also reported in the literature to deprotect WMK or derivative **2** but suffer of a lack of selectivity depending on the sensitivity of the substrates to acidic media.

During our studies, directed towards Mukaiyama-aldolisation of aliphatic aldehydes or corresponding dimethyl acetals with the silyl enol ether **3**, we applied the $FeCl_3.6H_2O$-catalyzed Rodríguez-Gimeno[11] conditions in dichloromethane. A quantitative deprotection of the cyclic ketal was observed at room temperature, affording after filtration over a pad of silica, a mixture of ketone **1** and the dioxolanes of the corresponding starting aldehydes or dimethyl acetals (figure 1). We supposed that an iron(III) transacetalization reaction occurred from **3** to aldehyde/dimethyl acetal reagents of the Mukaiyama-aldolisation. This equilibrated process should be driven by the higher electrophilicity of aldehydes compared to diketone **1**. Iron(III) chloride hexahydrate was already known as a deprotected catalyst of ketals or acetals as well as reagent of THP or MOM ethers cleavage, but often used in large excess (3.5 equiv.).[12] Iron(III) chloride adsorbed on silica gel was also known for selective deprotection of ketals or acetals in the presence of OAc, OBn and OTBDMS.[13] Recently, Sakiji's group reported an efficient cleavage of methoxyphenylmethyl-protected alcohols in excellent yields.[14] Moreover $FeCl_3$ can efficiently catalyze Boc deprotection of *N,N'*-diprotected amines.[15] In this context, we supposed that the use of a low molecular weight aldehyde as transacetalization partner with catalytic amount of non-toxic and readily available iron(III) salt

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should provide highly pure mother ketones, avoiding silica gel column chromatography. We describe herein the mild, efficient and chemoselective deprotection of acetals and ketals *via* transacetalization with acetaldehyde or propioanaldehyde in presence of iron(III) trichloride hexahydrate as the Lewis acid catalyst.

Our pre-examination indicated that only 10 mol % of iron trichloride could achieve deprotection of **2** in CH_2Cl_2. Therefore, we initially investigated the influence of the Lewis acid, acetaldehyde **4a** or propionaldehyde **4b** stoichiometry and the nature of solvent on the reaction rate using enone **2**[16] as substrate (table 1).

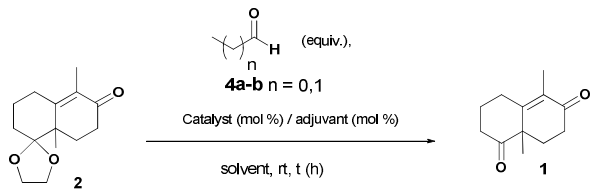
This first set of experiments determined that standard deprotection protocol involved preparing a solution of enone **2** with two equivalents of aldehydes **4a** or **4b** in dichloromethane, to which was added $FeCl_3.6H_2O$ (10 mol %) (entries 2 and 6). The resulting crude mixture was filtered over a pad of silica and concentrated under vacuum to afford pure diketone **1**. The use of one equivalent of aldehyde **4b** led also to a total conversion but the volume of aldehyde to handle was not adapted to the scale (0.2 to 1 mmol) (entry 7). As expected from literature,[12] a nasty deprotection occurred in the absence of aldehydes **4a-b** (entry 1). The reaction can be performed without any solvent, using an excess (10 equiv.) of aldehyde **4a** (entry 8) which clearly shows that the deprotection is undoubtedly proceeding *via* a transacetalization reaction. ^{1}H NMR monitoring of the reactions revealed the concomitant formation of the corresponding acetaldehyde dioxolane. Deprotection occurred quantitatively even with only 1 % mol of catalyst but required longer reaction time (30h, entry 3). Since aqueous solutions of $FeCl_3$ contain a mixture of the weakly acidic hydrates $[Fe(H_2O)_6]_3^+$ and $[Fe(H_2O)_5(OH)]_2^+$ able to catalyze the reaction,[12] we applied our standard conditions in the presence of 10 mol % of 2,6-di*tert*-butylpyridine (DTBP) as proton scavenger or by using anhydrous $FeCl_3$. No change was observed when anhydrous $FeCl_3$ was used as catalyst (entry 4), but addition of the proton scavenger to $FeCl_3.6H_2O$ provided a weaker deprotecting agent (entry 5), since quantitative deprotection was observed only after 8 hours.

Inspired by a paper reporting mild and selective acetals and ketals deprotection using $In(OTf)_3$ (1 mol %)-catalyzed transacetalization in acetone,[17] we attempted $FeCl_3.6H_2O$-catalyzed deprotections in the same solvent (entries 9, 10, 11).

No significative change was observed in acetone and in the presence of acetaldehyde **4a** (entries 2 and 9). In sharp contrast, the lack of aldehyde lead to significantly longer reaction time (entry 10) and higher temperature was required to complete the reaction within two hours (entry 11). This is easily explained by the lower electrophilicity of acetone compared to acetaldehyde **4a**.

In order to compare the catalytic activity of $FeCl_3.6H_2O$ and $In(OTf)_3$, we performed a set of experiments using 1 or 10 % mol of $In(OTf)_3$). Application of Gregg *et al.* conditions[17], in acetone using 1 mol % of $In(OTf)_3$ gave rise to 75% of conversion after 24 h (entry 12).

Table 1. $FeCl_3.6H_2O$-catalyzed transacetalization deprotection of enone **2**[a].



Entry	Aldehyde **4a-b** (n= 0 or 1)	Catalyst (mol %) / Adjuvant (mol %)	Solvent	t (h)[b]	Yield (%)[c]
1	-	$FeCl_3.6H_2O$ (10)	DCM	3	Complex mixture
2	**4a** (2.0)	$FeCl_3.6H_2O$ (10)	DCM	1.5	99
3	**4a** (2.0)	$FeCl_3.6H_2O$ (1)	DCM	30	99
4	**4a** (2.0)	$FeCl_3$ (10)	DCM	2	97
5	**4a** (2.0)	$FeCl_3.6H_2O$ (10) /DTBP (10)	DCM	8	99[d]
6	**4b** (2.0)	$FeCl_3.6H_2O$ (10)	DCM	2	99
7	**4b** (1.0)	$FeCl_3.6H_2O$ (10)	DCM	2	94
8	**4a** (10.0)	$FeCl_3.6H_2O$ (10)	Neat	8	99
9	**4a** (2.0)	$FeCl_3.6H_2O$ (10)	Acetone	2	99
10	-	$FeCl_3.6H_2O$ (10)	Acetone	24	97
11	-	$FeCl_3.6H_2O$ (10)	Acetone	2	97[e]
12	-	$In(OTf)_3$ (1)	Acetone	24	75
13	-	$In(OTf)_3$ (10)	Acetone	24	97
14	**4a** (2.0)	$In(OTf)_3$ (10)	DCM	0.5	99
15	-	$In(OTf)_3$ (10) /DTBP (1 equiv)	Acetone	6 days	0[d]
16	**4a** (2.0)	$In(OTf)_3$ (10) /DTBP (10)	DCM	4.5	98[d]
17	**4a** (2.0)	- /Triflic acid (10)	DCM	0.25	97

[a]General conditions: substrate **2** (1 mmol), aldehyde **4a** (2 mmol), $FeCl_3$. H_2O (10 mol %), DCM (2 mL) at rt. [b]Reaction time needed to observe complete disappearance of starting material (monitored by GC or ^{1}H NMR). [c]Isolated yields. [d] DTBP=2,6-di*tert*-butylpyridine [e]At reflux in a sealed-tube.

The latter can be improved to 97% when using 10 % mol of $In(OTf)_3$ (entry 13). Applying our reaction conditions to $In(OTf)_3$ lead to complete deprotection within 30 min (entry 14). Addition of 1 equiv. of 2,6-di*tert*-butylpyridine as proton scavenger in the conditions described by Gregg et al.[17] inhibited the reaction and no deprotection was observed even after 6 days (entry 15). Finally, 10 mol % of $In(OTf)_3$ in the

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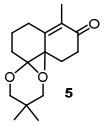
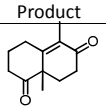
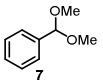
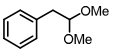
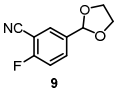
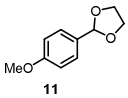
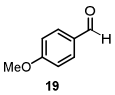
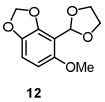
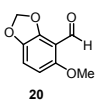
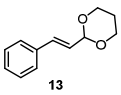
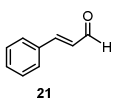
presence of 10 mol % of 2,6-di*tert*-butylpyridine and 2 equiv. of acetaldehyde in dichloromethane required longer time (4.5h *versus* 0.5h) to afford a complete deprotection after 24h (entry 14 and entry 16). It has to be noted that the use of 10 mol % of triflic acid as sole catalyst in the presence of 2 equiv. acetaldehyde in dichloromethane afforded a complete deprotection within 15 minutes (entry 17).

The versatility of this transacetalization protocol[18] ($FeCl_3.6H_2O$ (10 mol %)/acetaldehyde **4a** (2 equiv.)) was demonstrated by the quantitative deprotection of different ketals **5-6** or acetals **7-13** with electron-rich, electron-poor aromatic substrate, sensitive heteroaromatic or sterically hindered substrates to the corresponding carbonyl compounds (table 2).

Table 2. Substrate scope for the deprotection of several ketals/acetals **5-13** by $FeCl_3.6H_2O$/acetaldehyde **4a**[a]

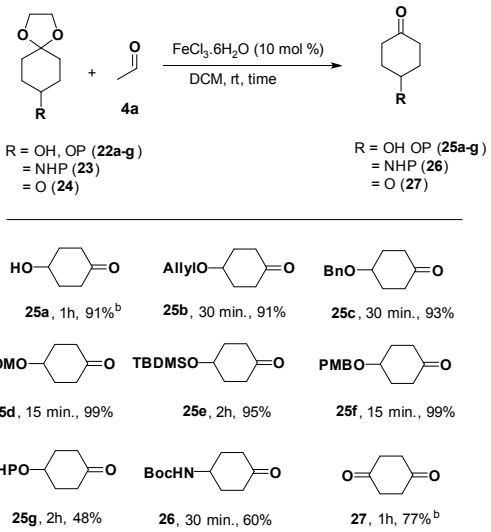
Entry	Substrate	T (°C), t (h)	Product	Yield (%)
1	 **5**	rt, 0.25	 **1**	99[b]
2	 **6**	reflux, 1	 **14**	99[b]
3	 **7**	rt, 0.25	 **15**	99[b]
5	 **8**	rt, 1	 **16**	76[c]
6	 **9**	rt, 0.25	 **17**	95[b]
7	 **10**	rt, 0.25	 **18**	90[b]
8	 **11**	rt, 0.25	 **19**	98[b]
9	 **12**	rt, 0.25	 **20**	98[b]
10	 **13**	rt, 0.25	 **21**	98[b]

[a] Reaction conditions: substrates **5-13** (0.5 mmol), acetaldehyde **4a** (1 mmol), $FeCl_3.6H_2O$ (10 mol %), DCM (1 mL) at rt. [b]Isolated yields. [c]^{1}H NMR conversion.

The dioxane functionality or pinacol acetals which are typically difficult to remove under mild conditions,[7,19] were effectively hydrolyzed with $FeCl_3.6H_2O$ (10 mol %)/acetaldehyde **4a** (2 equiv.) as demonstrated by the quantitative deprotection of the cyclic ketals **5, 6** and **13** (entries 1, 2 and 10). Moderate conversion was obtained with aliphatic acetal **8**, since the corresponding aldehyde electrophilicity is close to acetaldehyde (entry 5). As a consequence an equilibrium between the protected and deprotected form is observed with time.

The mild, neutral conditions found when using our $FeCl_3.6H_2O$ (10 mol %)/acetaldehyde **4a** (2 equiv.) system tolerate a wide range of functional groups including acid sensitive TBDMS-allyl- MOM-, benzyl- THP- and PMB ethers, **22b-g**, **23** and **24** (table 3). In the case of silyl ether **25e**, the reaction had to be monitored since a Si-O bond cleavage started to appear after two hours leading to the corresponding keto-alcohol after 3 hours. Competitive THP ether cleavage was also observed during the deprotection of **22g** and the ketone **25g** was obtained in 48% isolated yield.

Table 3 Chemoselective substrate scope for the deprotection of dioxane **22a-g, 23** and **24** with $FeCl_3.6H_2O$/acetaldehyde **4a** system[a]



[a]Reaction conditions: substrates **22a-g**, **23** and **24** (0.5 mmol), acetaldehyde **4a** (1 mmol), $FeCl_3.6H_2O$ (10 mol %), DCM (1 mL) at rt. [b]Conversion are consigned since compounds **25a** and **27** are volatiles.

Selective deprotection of the *N*-Boc-aminoketal **23** was observed and the corresponding *N*-Boc-aminoketone **26** was isolated in 60% yield after 30 minutes at rt. Surprisingly, longer reaction time, higher temperature or the use of larger amount of catalyst did not improve the yield, and no further *N*-Boc deprotection was observed. Diketone **24**, protected with one dioxolane was efficiently deprotected in a reasonable time (1h) in good yield with the same amount.

Finally, this protocol tolerates acid sensitive tertiary alcohols as exemplified by scheme 1, where **28** is quantitatively deprotected at 0 °C to the ketone **29** without any formation of the conjugated double-bond (scheme 1). It is to note that **28** was however completely converted to conjugated ketone by raising temperature to rt.

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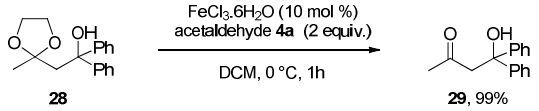

Scheme 1: Chemoselective deprotection of aliphatic ketone **28** with $FeCl_3.6H_2O$/acetaldehyde **4a** system.

In summary, $FeCl_3.6H_2O$ (10 mol %)/acetaldehyde (2 equiv.) catalyzed ketals/acetals cleavage in DCM or acetone represents a mild, efficient, environmentally friendly and cheap deprotection reaction. It relies on the transacetalization from ketals/acetals to the volatile acetaldehyde/propionaldehyde acetal which can be easily removed by evaporation. This reaction is driven by the difference of electrophilicity of aldehyde and ketone in favour of aldehyde. This very simple procedure do not required anhydrous solvent nor argon atmosphere, and proceeds at room temperature. No work up or further purification is needed; a simple filtration over a pad of silica to remove the iron salt and evaporation of volatile acetal of acetaldehyde provides pure deprotected ketone. Considering the high chemoselectivity towards acido-labile ether protected groups, and *N*-Boc protected groups, these conditions can be efficiently applied to total synthesis.

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Notes and references

1 *(a)* J. R. Hanson, *Nat. Prod. Rep.*, 2015, **32**, 1654–1663; *(b)* T. Hao-Yu, Y. Xia, Z. Cheng-Chen, J. Qian and G. Jin-Ming, *Curr. Med. Chem.*, 2015, **22**, 2375-2391; *(c)* R. E. Ireland, *J. Am. Chem. Soc.*, 1970, **92**, 5743–5746; *(d)* G.-M. Xue, Y.- Z. Xia, Z.-M. Wang, L.-N. Li, J.-G. Luo and L.-Y. Kong, *Eur. J. Med. Chem.,* 2016, **121**, 238-249.

2 *(a)* B. Bradshaw and J. Bonjoch, *Synlett*, 2012, **23**, 337–356. (*b*) T. Wu, Q. Wang, C. Jiang, S. L. Morris-Natschke, H. Cui, Y. Wang, Y. Yan, J. Xu and Q. Gu, *J. Nat. Prod.,* 2015, **78**, 500-509; (*c*) A. K. Cheung, R. Murelli and M. L. Snapper, *J. Org. Chem*., 2004, **69**, 5712-5719; (*d*) Y. Fukui, K. Narita and T. Katoh, *Chem. Eur. Joc.,* 2014, **20**, 2436-2439.

3 *(a)* G. Villa, B. Bradshaw, C. Bürki, J. Bonjoch and P. Renaud, *Tetrahedron Lett.*, 2014, **55**, 4608–4611; (*b*) J. Sakurai, T. Kikuchi, O. Takahashi, K. Watanabe and T. Katoh, *Eur. J. Org. Chem*., 2011, **16**, 2948–2957; (*c*) H. Hagiwara and H. Uda, *J. Org. Chem*., 1988, **53**, 2308–2311.

4 A. K. Banerjee and M. Laya-Mimo, *Studies in Natural Products Chemistry*, 2000, **24**, 175-213.

5 *(a)* P. G. M. Wuts and T. W. Greene, in *Greene's Protective Groups in Organic Synthesis*, Wiley, New York, 4th edn, 2006; (*b*) F. A. Meskens, *Synthesis*, 1981, 501-522; (*c*) M. Schelhaas and H. Waldmann, *Angew. Chem., Int. Ed. Engl*., 1996, **35**, 2056-2083.

6 *(a)* E. Marcantoni and F. Nobili*, J. Org. Chem.*, 1997, **62**, 4183-4184; (*b*) U. Yutaka, N. Koumoto and J. Fujisawa, *Chem. Lett.*, 1989, 1623-1626; (*c*) J. Sun, Y. Dong, L. Cao, X. Wang, S. Wang and Y. Hu, *J. Org. Chem.*, 2004, **69**, 8932-8934; (*d*) S. H. Lee, J. H. Lee and C. M. Yoon, *Tetrahedron Lett.*, 2002, **43**, 2699-2703; *(e)* R. Dalpozzo, A. D. Nino, L. Maiuolo, A. Procopio, A. Tagarelli, G. Sindona and G. Bartoli, *J. Org. Chem.*, 2002, **67**, 9093-9095; *(f)* R. Kumar, D. Kumar and A. K. Chakraborti, *Synthesis*, 2007, **2**, 299-303; *(g)* M. Lakshmi Kantam, V. Neeraja and P. Sreekanth, *Catal. Comm*., 2001, **2**, 301-304.

7 *(a)* A. Ates, A. Gautier, B. Leroy, J.-M. Plancher, Y. Quesnel and, I. E. Markó, *Tetrahedron Lett.,* 1999, **40**, 1799–1802; (*b*) I. E. Markó, A. Ates, A. Gautier, B. Leroy, J.-M. Plancher, Y. Quesnel and J.-C. Vanherck, *Angew. Chem. Int. Ed.,* 1999, **38**, 3207–3209; (*c*) A. Ates, A. Gautier, B. Leroy, J.-M. Plancher, Y. Quesnel, J.-C. Vanherck and I. E. Markó, *Tetrahedron,* 2003, **59**, 8989–8999.

8 D. A. Lanfranchi, N. Baldovini and G. Hanquet, *Synthesis,* 2008, **23**, 3775– 3778.

9 T. Katoh, M. Nakatani, S. Shikita, R. Sampe, A. Ishiwata, O. Ohmori, M. Nakamura and S. Terashima, *Org. Lett.,* 2001, **3**, 2701-2704.

10 *(a)* B. Schmalzbauer, J. Herrmann, R.Muller and D. Menche, *Org. Lett.,* 2013, **15**, 964-967; (*b*) J. Sakurai, T. Oguchi, K. Watanabe, H. Abe, S. Kanno, M. Ishikawa and T. Katoh, *Chem. Eur. J.,* 2008, **14**, 829–837.

11 A. Rodríguez-Gimeno, A. B. Cuenca, J. Gil-Tomás, M. Medio-Simón, A. Olmos and G. Asensio, *J. Org. Chem*., 2014, **79**, 8263−8270.

12 S. E. Sen, S. L. Roach, J. K. Boggs, G. J. Ewing and J. Magrath, *J. Org. Chem*., 1997, **62**, 6684-6686.

13 (*a*) K. S. Kim, Y. H. Song, B. H. Lee and C. S. Hahn, *J. Org. Chem.,* 1986, **51**, 404-407; (*b*) A. Descomps and R. Carlson, *Synth. Comm.,* 2014, **44**, 757-761.

14 Y. Sawama, M. Masuda, S. Asai, R. Goto, S. Nagata, S. Nishimura, Y. Monguchi and H. Sajiki, *Org. Lett*., 2015, **17**, 434-437.

15 J. M. López-Soria, S. J. Pérez, J. N. Hernández, M. A.; Ramírez, V. S. Martín and J. I. Padrón, *RSC Adv.,* 2015, **5**, 6647–6651.

16 Protection of diketone **1** as dioxolane **2** is widely described in the literature. Nevertheless in our hands these conditions lead to formation of small amount of bis-protected product or not complete conversion of starting material which were difficult to

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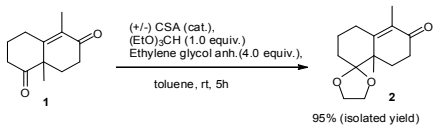
separate. Strict application of the conditions depicted in the scheme below afforded quantitatively the ketone **2**.



See (a) S. Poigny, M. Guyot and M. J. Samadi, *J. Org. Chem.,* 1998, **63**, 5890-5894; *(b)* M. E. Jung and B. A. Duclos, *Tetrahedron,* 2006, **62**, 9321-9334; *(c)* T. Ling, J. Xu, R. Smith, A. Ali, C. L. Cantrell and E. A. Theodorakis, *Tetrahedron*, 2011, **67**, 3023-3029; *(d)* M. Scheck, M. A. Koch and H. Waldmann, *Tetrahedron*, 2008, **64**, 4792-4802.

17 B. T. Gregg, K. C. Golden and J. F. Quinn, *J. Org. Chem.,* 2007, **72**, 5890–5893.

18 Typical procedure: Acetal/ketal (1 mmol, 1 equiv.) was dissolved in DCM (2 mL). Acetaldehyde **4a** (2 equiv.) was added followed by the addition of $FeCl_3.6H_2O$ (0.1 equiv.). The resulting colored (yellow to brown) reaction mixture was stirred at r.t. until completion (^{1}H NMR or GC monitoring), then filtered over a pad of silica gel (1 cm thick, DCM), eluted with DCM and evaporated to get the pure product.

19 (*a)* J. C. Stowell and D. R. Keith, *Synthesis* 1979, 132-133, *(b)* Y. Seeleib, G. Nemecek, D. Pfaff, B. D. Süveges and J. Podlech, *Synth. Commun*., 2014, **44**, 2966-2973.