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Syn diastereoselectivity in the synthesis of homoallylamine using crotylsilane in the three-component reaction

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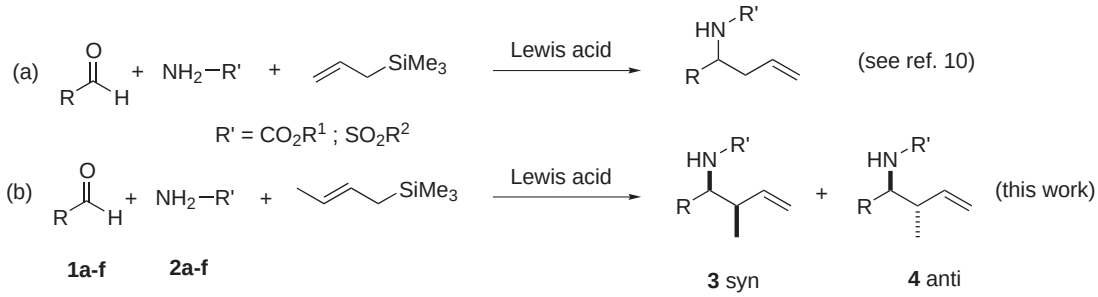
Abstract—Crotylsilane was used in a three-component reaction for the synthesis of homoallylamines from aldehydes. A moderate to good *syn*/*anti* 5/1 diastereoselectivity was observed. The obtained homoallylamines were transformed into pyrrolidines or piperidines.

Homoallylamines are useful intermediates for the construction of bioactive substances,[1–9] and rapidly accessible by a three-component reaction recently developed by Veenstra[10] and pioneered by Panek.[11] In this reaction an acyliminium, formed in situ by the mixture of an aldehyde and a primary carbamate, is submitted to a nucleophilic attack of trimethylallylsilane (reaction (a) in Scheme 1). As we were involved in the utilization of allylsilanes in the preparation of azaheterocycles,[12] this convenient procedure attracted our attention. We decided to address the following questions: what would be the diastereoselectivity if crotylsilane[13] was used instead of allylsilane (reaction (b) in Scheme 1)? In this letter we present our preliminary results on the preparation of methylated homoallylamines followed by their transformation in pyrolidines and piperidines.

In order to optimize the reaction conditions, a screening was performed on several parameters such as solvents, Lewis acids or carbamate structures. For these purposes benzaldehyde (**1a**) was used as a model. Our results are collected in Table 1. Among the conditions tested $TiCl_4$ in CH_3CN with the benzylcarbamate (**2a**) gave the best yield for the chemical transformation (entry 6), however the diastereoselectivity was modest: *syn*/*anti*: 3/1.[14] The change from a bi- to a monodentate Lewis acid has a favorable effect on the diastereoselectivity that was increased to 5/1 (compare entry 2 and 4 to entry 6). The benzaldehyde dimethylacetal (**1b**) was found also to be a suitable substrate for crotylsilane (entries 13–16). The switch to other appendages attached on nitrogen such as Fmoc or Tosyl group did contribute to any change in the *syn*/*anti* ratio (entries 17–21), except for nosyl group (**2f**) where the homoallylalcohol was obtained!

As exemplified (entries 22–25) the three-component reaction is suitable for other aldehydes (**1c**–**1f**) with



Scheme 1.

Keywords: crotylsilane; three-component; homoallylamines; iminiums; pyrrolidines; piperidines.

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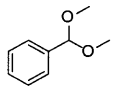
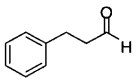
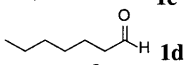
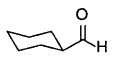
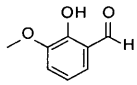
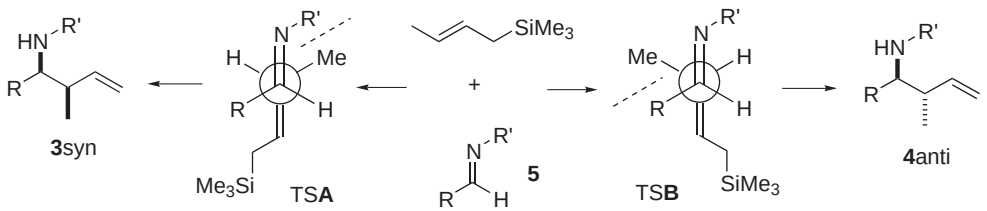
Table 1.

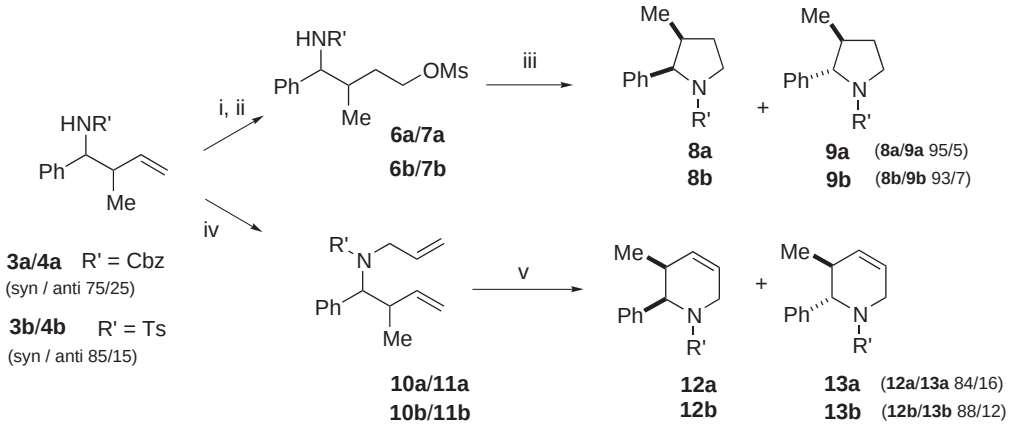
Entry	Aldehyde	Carbamate or Sulfonamide	Lewis acid	Solvent	Yield% (a)	**3 / 4** *syn / anti* (b)
1	benzaldehyde	Cbz-NH_2	$BF_3.OEt_2$	CH_2Cl_2	51	63/37
	1a	**2a**				
2	**1a**	**2a**	$BF_3.OEt_2$	CH_3CN	62	84/16(d)
3	**1a**	**2a**	TMSOTf	CH_2Cl_2	46	67/33
4	**1a**	**2a**	TMSOTf	CH_3CN	50	80/20
5	**1a**	**2a**	$TiCl_4$	CH_2Cl_2	0 (c)	-
6	**1a**	**2a**	$TiCl_4$	CH_3CN	82	73/27
7	**1a**	**2a**	$ZrCl_4$	CH_3CN	60	72/28
8	**1a**	**2a**	$Cu(OTf)_2$	CH_3CN	45	73/27
9	**1a**	**2a**	$Sc(OTf)_3$	CH_3CN	20	77/23
10	**1a**	**2a**	$AlCl_3$	CH_3CN	16	70/30
11	**1a**	**2a**	$Ti(O\text{-}iPr)_4$	CH_3CN	0 (c)	-
12	**1a**	**2a**	$Zn(OTf)_2$	CH_3CN	0 (c)	-
13	 **1b**	**2a**	$BF_3.OEt_2$	CH_2Cl_2	26	65/35
14	**1b**	**2a**	$BF_3.OEt_2$	CH_3CN	96	80/20
15	**1b**	**2a**	TMSOTf	CH_2Cl_2	46	67/33
16	**1b**	**2a**	TMSOTf	CH_3CN	56	65/35
17	**1a**	Tos-NH_2 **2b**	$BF_3.OEt_2$	CH3CN	67	84/16
18	**1a**	Boc-NH_2 **2c**	$BF_3.OEt_2$	CH_3CN	68	75/25
19	**1a**	Ms-NH_2 **2d**	$BF_3.OEt_2$	CH_3CN	63	77/23
20	**1a**	Fmoc-NH_2 **2e**	$BF_3.OEt_2$	CH_3CN	40	77/23
21	**1a**	Nos-NH_2 **2f**	$BF_3.OEt_2$	CH_3CN	40	alcohol
22	 **1c**	**2a**	$BF_3.OEt_2$	CH_3CN	79	85/15
23	 **1d**	**2a**	$BF_3.OEt_2$	CH_3CN	80	80/20
24	 **1e**	**2a**	$BF_3.OEt_2$	CH_3CN	75	80/20
25	 **1f**	**2a**	$BF_3.OEt_2$	CH_3CN	70	76/24

(a) yield after chromatography (silicagel Et_2O/hexane), (b) the ratio was determined by ^1H NMR, (c) no reaction, (d) typical procedure (entry 14): **1b** (1 eq), 0.13 M in CH_3CN, 0 °C, **2a** (1 eq), crotylsilane (1 eq) than $BF_3.OEt_2$ (1 eq), 0 °C to rt, 2h.

comparable results. From this preliminary exploration, it appears that the best experimental conditions to run the reaction were: acetonitrile (as solvent), $BF_3{\cdot}Et_2O$ (as Lewis acid) and benzylcarbamate (**2a**), and interestingly the reaction can be run at room temperature.



Scheme 2.



Scheme 3. Reagents and conditions: (i) (1) 9-BBN, THF, rt, 8 h, (2) NaOH, H_2O_2, 0°C, 2 h; (ii) MsCl, Et_3N, DMAP, CH_2Cl_2, 0°C to rt, yield 53% for two steps (**a** or **b**); (iii) NaH, DMF, 0°C to rt, **8a**/**9a** 93%, **8b**/**9b** 60%; (iv) NaH, DMF, 0°C then allylbromide, 80% for both; (v) Grubb's catalyst 5%, CH_2Cl_2, rt, 10 h, **12a**/**13a** 99%, **12b**/**13b** 95%.

The S_E2' reaction of an allylsilane to a carbonyl system, assisted by a Lewis acid is best described by a transition state where the geometry of the π-systems is antiperiplanar, and the diastereoselection is predicted with the Cram's rule (or its chelation counterpart).[15,16] Accordingly to explain the observed *syn* diastereoselectivity, transition state TS**A** (Scheme 2) accounts for the production of the major *syn* adduct **3** (*Re* face for the imonium, *Si* face for the allylsilane), whereas TS**B** would lead to the *anti* adduct **4** (*Re* face for the imonium, *Re* face for the allylsilane). Our results are in line with Chan's report on the reaction of crotylallylindenium reagents to iminiums,[17] but in contradiction with Masuyama on the addition of crotylsilane to an in situ formed *N*-tosyl-iminium.[18]

At first in both TS**A** or TS**B** severe steric interactions are apparent, in contrast to the similar picture with the corresponding aldehydes where TS**A** (*Re*, *Si*) is always less cruded.[16] What is the explanation for this *syn* preference in the allylation of iminiums and why is the diastereoselectivity comparable to the corresponding reaction with aldehydes? By molecular modeling it is apparent that the carbamate or the tosyl groups are mainly located out of the plane formed by the imine function, and on the top of the nitrogen atom, leaving some room on the both sides. Additionally as the Lewis acid is mediating its activation by chelation on the heteroatoms of the carbamate, the imine will lose partially its sp^2 character, and therefore its substituent will again have room on both sides of the nitrogen atom. Therefore the steric congestion may originate mainly from the interaction of the alkyl rest R (from the aldehyde) present on the iminium and the methyl from the crotylsilane (see TS**B**). This explanation is partly supported by the poor influence observed by larger carbamate (or sulfonamide) on the diastereoselectivity (entries 17–21). Anyway it is rather surprising that the aldehydes and their corresponding iminiums have the same preference for the *syn* over the *anti* diastereomer in the allylation sequence induced by crotylsilane. But further work is needed to apprehend better the transition state in order to improve the diastereoselectivity.

These homoallylamines can be chemically exploited to rapidly synthesize nitrogen containing heterocycles (as depicted on Scheme 3). Interestingly the pyrrolidine mixture **8a**/**9a** was enriched in its *cis* adduct (*cis*/*trans*: 95/5)[19] during the three step sequence. The corresponding piperidines[19] **12a**/**13a** or **12b**/**13b** were obtained by using a methatesis strategy.[20,21] In this case the cyclic adducts have the same *cis*/*trans* ratio that the corresponding acyclic compounds.

In conclusion crotylsilane can be used in the three-component reaction for the production of homoallylamines from a variety of aldehydes. The observed diastereoselectivity is moderate to good but further improvements are desirable. Nevertheless they are suitable adducts to a simple conversion into substituted pyrrolidines or piperidines.

Acknowledgements

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19. Selected physical data: **8a**/**9a** ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.66 (d, $J=6.9$ Hz, 3H, Me **8a**), 1.11 (d, $J=6.6$ Hz, 3H, Me **9a**), 1.57–1.79 (m, 1H), 1.92–2.05 (m, 1H), 2.34–2.60 (m, 1H), 3.56 (ddd, $J_1=10.9$ Hz, $J_2=7.2$ Hz, 1H), 3.78–3.85 (m, 1H), 4.95–5.18 (m, 3H), 6.81–6.84 (m, 1H), 7.07–7.31 (m, 8H). **8b**/**9b** ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.56 (d, $J=6.9$ Hz, 3H, Me **8b**), 0.81 (d, $J=6.5$ Hz, 3H, Me **9b**), 1.65–1.76 (m, 1H), 1.82–1.90 (m, 1H), 2.05 (s, 3H), 2.12–2.21 (m, 1H), 3.36 (ddd, $J_1=10.3$ Hz, $J_2=6.5$ Hz, 1H), 3.70 (ddd, $J_1=9.7$ Hz, $J_2=8.1$ Hz, $J_3=1.9$ Hz, 1H), 4.33 (d, $J=8.1$ Hz, 1H), 7.10–7.13 (m, 2H), 7.22–7.26 (m, 5H), 7.65 (d, $J=9.0$ Hz, 2H). **12a**/**13a** ^{1}H NMR (300 MHz, CD_3COCD_3): δ 0.84 (d, $J=7.5$ Hz, 3H, Me **12a**), 1.19 (d, $J=6.9$ Hz, 3H, Me **13a**), 287–2.90 (m, 1H), 3.67–3.73 (m, 1H), 4.26–4.33 (m, 1H), 5.04–5.35 (m, 3H), 5.60–5.95 (m, 2H), 7.25–7.31 (m, 10H). **12b**/**13b** ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.80 (d, $J=9.0$ Hz, 3H, Me **12b**), 1.19 (d, $J=6.8$ Hz, 3H, Me **13b**), 2.33 (s, 3H), 2.87–2.94 (m, 1H), 3.51–3.59 (m, 1H), 4.15–4.24 (m, 1H), 5.16 (d, $J=6.8$ Hz, 1H), 5.67–5.79 (m, 2H), 7.07 (d, $J=7.9$ Hz, 2H), 7.06–7.20 (m, 5H), 7.42 (d, $J=8.0$ Hz, 2H).
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