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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 15 (2004) 3703–3706

Chemoselective, accelerated and stereoselective aza-Michael addition of amines to *N*-phenylmaleimide by using TMEDA based receptors

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Received 23 August 2004; accepted 4 October 2004
Available online 5 November 2004

Abstract—An aza-Michael addition between a maleimide and amines is described in which the presence of simple amine receptors (TMEDA or *trans*-TMCDA) promote the chemoselectivity of the reaction (respectively, 1,2- and 1,4-addition). Additionally, both receptors are able to accelerate the reaction. Stoichiometries of complexes between receptors and amines were determined by ^{1}H NMR dilution experiments while enantiomeric excesses were observed on 1,4-adducts by using (1*R*,2*R*)-TMCDA.

1. Introduction

Chemists working in the biomimetic chemistry field conceive new substances and reactions, which imitate biological chemistry and expand the scope of chemistry. Enzymes are not only able to catalyze a wide range of reactions, but also control their chemo- and/or stereochemical outcomes. Hence, synthetic chemists have designed a variety of unnatural systems that mimic enzymes.[1]

For several years, we have been interested in the synthesis of new flexible receptors[2] for amines, acids or both acids and amines with the view to facilitate the reaction leading to an amide. During the course of our investigations concerning synthetic receptors,[2b,c] we were especially interested in the synthesis of several 3-aminosuccinimides by using the enantioselective aza-Michael addition reaction starting from primary amines and *N*-substituted-maleimides. Over the course of our studies, Philp et al.[3] reported the ability of a bis(phosphine oxide) host to increase the rate of addition of 4-fluorobenzylamine to *N*-phenylmaleimide. This inspired us to develop new amine receptors, which could be useful tools in the synthesis of 3-aminosuccinimides.

Two recent reports of Takemoto et al.[4] concerning the addition reaction of malonates to nitroolefins[4a] and nitroalkanes to imines[4b] by using a relatively sophisticated thiourea receptor having a 1,2-cyclohexyldiamine moiety, prompted us to describe our own results. Herein, we report the study of commercially available TMEDA and *trans*-*N*,*N*,*N*′,*N*′-tetramethylcyclohexanediamine (*trans*-TMCDA, Fig. 1) used as new receptors in the aza-Michael addition reaction of several primary amines, principally benzylamine derivatives, to *N*-phenylmaleimide (Scheme 1).

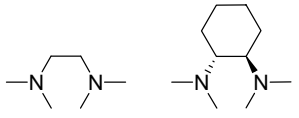

Figure 1. Receptors used.

2. Results and discussion

The aza-Michael addition reaction was conducted under the same conditions as described by Philp et al.[3] with the aim of comparing the efficiency of our receptors. Thus, *N*-phenylmaleimide **1** and amine **2a**, both at 50 mM in $CDCl_3$, were reacted at 40 and 21 °C. The

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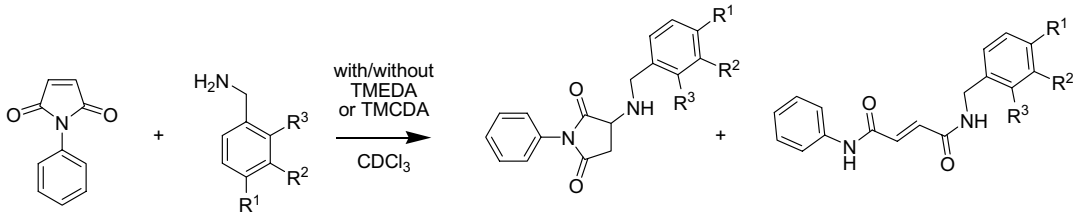
doi:10.1016/j.tetasy.2004.10.006



1

2a: $R^1 = F$, $R^2 = R^3 = H$
2b: $R^1 = R^2 = R^3 = H$
2c: $R^1 = CH_3$, $R^2 = R^3 = H$
2d: $R^1 = OCH_3$, $R^2 = R^3 = H$
2e: $R^1 = H$, $R^2 = CH_3$, $R^3 = H$
2f: $R^1 = R^2 = H$, $R^3 = CH_3$

3a: $R^1 = F$, $R^2 = R^3 = H$
3b: $R^1 = R^2 = R^3 = H$
3c: $R^1 = CH_3$, $R^2 = R^3 = H$
3d: $R^1 = OCH_3$, $R^2 = R^3 = H$
3e: $R^1 = H$, $R^2 = CH_3$, $R^3 = H$
3f: $R^1 = R^2 = H$, $R^3 = CH_3$

4a: $R^1 = F$, $R^2 = R^3 = H$
4b: $R^1 = R^2 = R^3 = H$
4c: $R^1 = CH_3$, $R^2 = R^3 = H$
4d: $R^1 = OCH_3$, $R^2 = R^3 = H$
4e: $R^1 = H$, $R^2 = CH_3$, $R^3 = H$
4f: $R^1 = R^2 = H$, $R^3 = CH_3$

Scheme 1. Reaction scheme for the aza-Michael addition reaction.

formation of products **3a** and **4a** was monitored by using 300 MHz ^{1}H NMR spectroscopy and the concentrations determined from these data.

The kinetic data at 40 °C depicted in Figure 2 show that almost the same amount of compounds **3a** and **4a** is formed and the rate of the reaction is very slow under these conditions. Thus, we first attempted to add 1 equiv of TMEDA to the reaction and observed an interesting improvement in the rate of formation concerning the 1,2-addition compound **4a** (Fig. 2). This interesting result led us to find another receptor with a structure based on TMEDA. Hence, we looked for a receptor that was either commercially available or with no more than one step to synthesize. We found that *trans*-TMCDA was the best candidate to fit all these conditions.[5] We decided to perform the reaction with *trans*-TMCDA under the same conditions as above. Surprisingly, we observed that, in this case, more of 1,4-addition compound **3a** was obtained than without *trans*-TMCDA both at 40 °C (Fig. 2) and 21 °C. These interesting results motivated us to investigate the control of chemoselectivity in this aza-Michael addition.

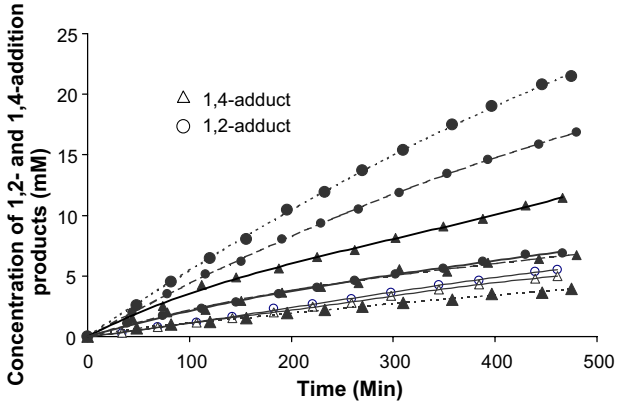


Figure 2. Kinetic data obtained for reaction between 4-fluorobenzylamine (50 mM) and *N*-phenylmaleimide (50 mM) at 40 °C in the absence of receptor (open symbols) and in the presence of TMEDA (filled symbols, long dashed lines for 1 equiv and small dashed lines for 0.25 equiv) or 1 equiv of *trans*-TMCDA (filled symbols, plain lines). Circles represent the concentration of the 1,2-addition product and triangles the concentration of the 1,4-addition product.

In the literature,[6] the presence of a catalytic amount of triethylamine is known to prompt some other Michael addition reactions and to play a role in their chemoselectivity. As a result, we decided to carry out a study on the influence of the amount of TMEDA and *trans*-TMCDA in the reaction between **1** and **2a** at 40 and 21 °C. The collected data at both temperatures clearly showed that by changing the amount of TMEDA, or *trans*-TMCDA the chemoselectivity of the reaction can be easily controlled. When the reaction is performed at 40 or 21 °C (Fig. 3) with 0.25 equiv. of TMEDA or *trans*-TMCDA, the rate for the 1,2-addition reaction leading to **4a** is increased, especially with TMEDA. At 40 °C, it is noteworthy that for 0.8 equiv of *trans*-TMCDA, an inversion in the chemoselectivity of the reaction was seen whilst no inversion was observed with TMEDA until 2 equiv. At 21 °C, an inversion occurred at 0.38 equiv with *trans*-TMCDA and 1.4 equiv with TMEDA.

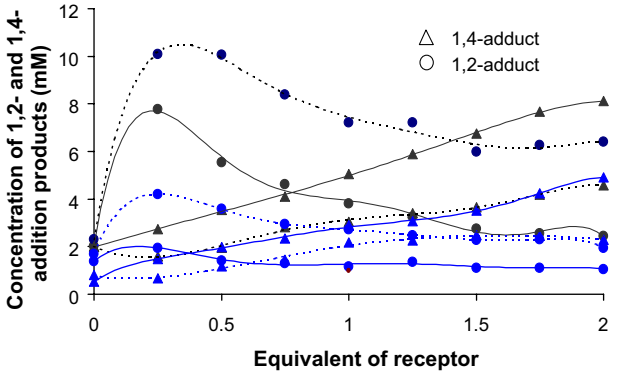


Figure 3. Data obtained after 180 min of reaction between 4-fluorobenzylamine (50 mM) and *N*-phenylmaleimide (50 mM) at 21 °C (blue) and 40 °C (black) in the presence of TMEDA (dashed lines) or *trans*-TMCDA (plain lines) as receptors. Circles represent the concentration of the 1,2-addition product and triangles the concentration of the 1,4-addition product.

These unexpected results are particularly interesting when compared to the bis(phophine oxide) host described by Philp and co-workers[3] who observed almost identical kinetic data and no changes in the chemoselectivity when the reaction was performed in the presence of 1 or 0.2 equiv of receptor. In our case, by using

Table 1. Concentrations (mM) of **3a–d** and **4a–d**, determined by ^{1}H NMR, obtained via Scheme 1 at 21 °C starting from **1** (50 mM) and **2a–d** (50 mM) after 24 h

Entry	Additive (equiv)	3a	4a	3b	4b	3c	4c	3d	4d
1	—	7.0	9.2	8.7	9.9	12.9	12.9	15.2	17.1
2	TMEDA (0.25)	4.8	21.3	9.3	22.0	13.8	24.3	15.4	25.2
3	*trans*-TMCDA (2)	18.2	1.6	25.4	2.5	30.1	3.0	37.5	3.0

0.25 equiv of TMEDA at 40 °C (Figs. 2 and 3) or 21 °C, we were able to favour predominantly the formation of the 1,2-addition compound **4a** while by using *trans*-TMCDA with more than 0.8 equiv at 40 °C or 0.38 equiv at 21 °C the 1,4-addition compound **3a** was obtained as the major product. To compare our results with those described by Philp,[3] we used 4-fluorobenzylamine **1** and obtained similar rate accelerations with the advantage of controlling the chemoselectivity of the reaction. We were interested in also knowing whether the results we obtained were a specificity of **1** due to the presence of the fluoro group. We decided to conduct the same kinetic study with several other benzylamine derivatives with 0.25 equiv of TMEDA and 2 equiv of *trans*-TMCDA at 21 °C to favour, respectively, 1,2- and 1,4-addition. Data collected after 24 h of reaction are presented in Table 1. The present results showed that, as we expected, the change in the chemoselectivity of the reaction for benzylamine derivatives **2b–d** is the same as the one observed with 4-fluorobenzylamine **2a** when TMEDA is replaced by *trans*-TMCDA. Then, even though TMEDA and *trans*-TMCDA have a very close structure, we observed a different behaviour during the course of the reaction.

We then decided to establish the stoichiometry of the complexes formed between amines (guests) and TMEDA or *trans*-TMCDA (hosts). A Job-plot[7] analysis of NMR spectroscopy titration experiments in $CDCl_3$ showed that TMEDA binds one amine **3a** (Fig. 4). The results were exactly the same when this experiment was conducted with other amines **3b–d** and phenethylamine. The association constants K_a were then determined assuming a 1:1 complexation process. K_a values of 400, 420, 470, 475 and 208 M^{-1} were obtained for **2a–d** and phenethylamine, respectively. The stoichiometry of complexation was also investigated using a Job-plot analysis between *trans*-TMCDA and amines **3a–d** or phenethylamine. However in this case, we observed that complexes (Fig. 5) were not 1:1 as expected but probably 1:4 (host/guest). At the moment, we do not have any explanation for this observation, but this finding could be a direction to follow to account for the different chemoselectivity between TMEDA and *trans*-TMCDA.

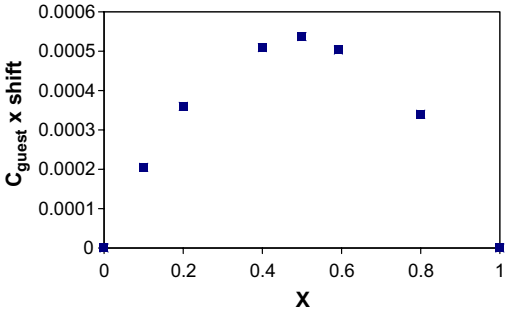


Figure 4. Job plot of TMEDA (host) with 4-fluorobenzylamine (guest). The sum of host and guest concentrations was constant ($C_0 = 0.0130\,mol\,L^{-1}$, guest concentration = xC_0) and the chemical shift of the NH_2 protons was monitored.

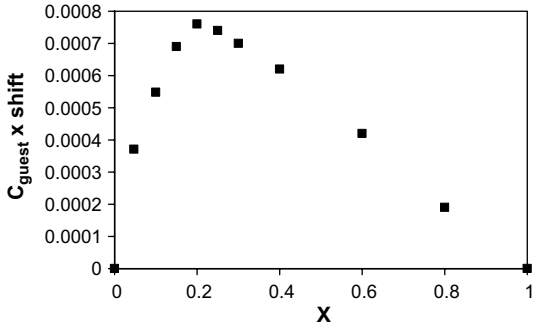


Figure 5. Job plot of *trans*-TMCDA (host) with 4-fluorobenzylamine (guest). The sum of host and guest concentrations was constant ($C_0 = 0.0130\,mol\,L^{-1}$, guest concentration = xC_0) and the chemical shift of the NH_2 protons was monitored.

The cyclohexane-1,2-diamine structural framework is often used as a ligand in asymmetric synthesis.[8] Encouraged by the above successful acceleration with *trans*-TMCDA in the formation of compounds **3a–f**, we turned our attention to the 1,4-enantioselective addition of amines to *N*-phenylmaleimide with (1*R*,2*R*)-TMCDA.[5] To study the enantioselectivity, we tested several different experimental conditions by changing

Table 2. Enantioselective addition of amines **2a**,**c**,**e** and **2f** to maleimide **1** with (1*R*,2*R*)-TMCDA after 24 h reaction at 21 °C

Entry	(1*R*,2*R*)-TMCDA (equiv)	Product	% Ee[a,b]	% Ee[a,c]	% Ee[a,d]
1	0.5	**3a**	16	9	7
2	2	**3c**	14	9	2
3	2	**3e**	14	4	2
4	1	**3f**	15[e]	6[e]	3[e]

[a] Ee's were measured by HPLC analysis using the chiral column, Daicel OD column for **3a** and **3c**[9a] and Daicel OJ column for **3e** and **3f**.[9b]

[b] Reaction run in $CHCl_3$.

[c] Reaction run in toluene.

[d] Reaction run in THF.

[e] The (*S*)-absolute configuration was assigned by comparison with the retention time measured by HPLC analysis[9b] with (*S*)-enantiopure analytical samples of **3f** prepared by reacting the 2-methylbenzaldehyde with (*S*)-3-amino-*N*-phenylsuccinimide[10] in EtOH followed by $NaBH_4$.

the amount of *trans*-TMCDA from 0.5 to 2 equiv, amines, solvents and temperature (21 and 40 °C). The main results at 21 °C are shown in Table 2, and although the enantiomeric excesses we obtained are modest, they are still significant.

The highest enantioselectivity was observed when the reaction was conducted in $CHCl_3$ with amines **2a**,**c**,**e** and **2f**. However, concerning amines **2b** and **2d**, we were unable to determine the enantiomeric excesses for **3b** and **3d**, while with phenethylamine or *tert*-butylamine, no excesses were observed.

3. Conclusion

In conclusion, TMEDA and *trans*-TMCDA are capable of accelerating the nucleophilic addition of an amine to a maleimide. The chemoselectivity of the reaction was also efficiently controlled either by the presence of TMEDA as a receptor of amines to promote the 1,2-addition reaction or by *trans*-TMCDA to favour the 1,4-addition reaction. The stoichiometry of complexation with amines showed the formation of two different complexes with TMEDA or *trans*-TMCDA. Finally, by using (1*R*,2*R*)-TMCDA, we obtained a low but interesting enantioselectivity in the formation of 3-aminosuccinimides. These preliminary results are very promising and the study of other Michael addition reactions is currently in progress in our laboratory.

Acknowledgements

This work was supported in part by the French Embassy in China and in part by 'Région Haute-Normandie'.

References

1. (a) Hartley, J. H.; James, T. D.; Ward, C. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3155–3184; (b) Rowlands, G. J. *Tetrahedron* **2001**, *57*, 1865–1882; (c) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481–2495; (d) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289–296.
2. (a) Charpentier, P.; Brière, J.-F.; Dupas, G.; Quéguiner, G.; Bourguignon, J. *Tetrahedron* **1996**, *52*, 10441–10454; (b) Brière, J.-F.; Charpentier, P.; Dupas, G.; Quéguiner, G.; Bourguignon, J. *Tetrahedron* **1997**, *53*, 2075–2086; (c) Brière, J.-F.; Dupas, G.; Quéguiner, G.; Bourguignon, J. *Tetrahedron* **2000**, *56*, 8679–8688; (d) Moore, G.; Levacher, V.; Bourguignon, J.; Dupas, G. *Tetrahedron Lett.* **2001**, *42*, 261–263; (e) Moore, G.; Papamicaël, C.; Levacher, V.; Bourguignon, J.; Dupas, G. *Tetrahedron* **2004**, *60*, 4197–4204.
3. Ashton, P. R.; Calcagno, P.; Spencer, N.; Harris, K. D. M.; Philp, D. *Org. Lett.* **2000**, *2*, 1365–1368.
4. (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673; (b) Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625–627.
5. We prepared *trans*-TMCDA and (1*R*,2*R*)-TMCDA starting from commercially available *trans*-diaminocyclohexane and (1*R*,2*R*)-diaminocyclohexane, respectively, by using a procedure closed to that described by Chooi, S. Y. M.; Tan, M. K.; Pak-Hing, L.; Mok, K. F. *Inorg. Chem.* **1994**, *33*, 3096–3103.
6. For example, see (a) Kamimura, A.; Murakami, N.; Yokota, K.; Shirai, M.; Okamoto, H. *Tetrahedron Lett.* **2002**, *43*, 7521–7523; (b) Kamimura, A.; Murakami, N.; Kawahara, F.; Yokota, K.; Omata, Y.; Matsuura, K.; Oishi, Y.; Morita, R.; Mitsudera, H.; Suzukawa, H.; Kakehi, A.; Shirai, M.; Okamoto, H. *Tetrahedron* **2003**, *59*, 9537–9546.
7. Job, A. *Ann. Chim. (10th series)* **1928**, *9*, 113–203.
8. For example, see: (a) Arena, C. G.; Casilli, V.; Faraone, F. *Tetrahedron: Asymmetry* **2003**, *14*, 2127–2131; (b) Calter, M. A.; Orr, R. K. *Tetrahedron Lett.* **2003**, *44*, 5699–5701; (c) Kizirian, J.-C.; Caille, J.-C.; Alexakis, A. *Tetrahedron Lett.* **2003**, *44*, 8893–8895; (d) Cabello, N.; Kizirian, J.-C.; Alexakis, A. *Tetrahedron Lett.* **2004**, *45*, 4639–4642.
9. General HPLC conditions: Spectra System P1000xR and AS3000 monitoring with a photo diod array; Wavelength used: 230 nm. (a) Daicel OD column (250 × 4.6 mm, 10 μL); **3a**, 1 mL min^{-1}, *i*-PrOH/heptane: 10:90 to 25:75 over 60 min; retention time = 45 and 48 min. **3c**, *i*-PrOH/heptane: 12:88; retention time = 42 and 47 min; (b) Daicel OJ column (250 × 4.6 mm, 10 μL); **3e**, 1 mL min^{-1}, *i*-PrOH/heptane: 28:72; retention time = 48 and 70 min. **3f**, *i*-PrOH/heptane: 28:72; retention time = 50 min (3*S* configuration) and 65 min.
10. Witiak, D. T.; Muhi-Eldeen, Z.; Mahishi, N.; Sethi, O. P.; Gerald, M. C. *J. Med. Chem.* **1971**, *14*, 24–30.