Functionalized Aminocyclopropanes From Functionalized Organozinc Compounds and *N*,*N*-Dialkylcarboxamides[1]

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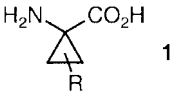
Received 15 February 2002

Abstract: Inter- as well as intramolecular competition experiments have been performed to demonstrate that *N*,*N*-dialkylcarboxamides react faster than *tert*-butyl esters with the titanium intermediates formed from ethylmagnesium bromide and methyltitanium triisopropoxide to selectively yield cyclopropylamines rather than cyclopropanols. Thus, functionalized organozinc reagents including a series with *tert*-butyl ester functionalities could be employed under newly developed conditions to transform *N*,*N*-dialkylformamides into chloroalkyl-substituted *N*,*N*-dialkylcyclopropylamines (55–67%) and *tert*-butyl (*N*,*N*-dialkylaminocyclopropyl)alkanoates (24–63% yield).

Key words: cyclopropanes, organometallics, amino acids, organotitanium intermediates, cyclopropylamines

Quite a number of cyclopropyl-group containing amino acids occur in nature, and most of them have important biological activities. The simplest one, 1-aminocyclopropanecarboxylic acid **1** (R = H) is abundant as the natural precursor to the plant growth hormone ethylene,[2] and derivatives such as **1** (R = Me, Et) are potent inhibitors of the ethylene forming enzyme (Figure). Aminocyclopropane moieties are also essential in many pharmacologically relevant compounds such as the widely used broad-spectrum antibiotics ciprofloxacin (Ciprobay®) and moxifloxacin (Avalox®). Our previously reported adaptation of the Kulinkovich protocol for the conversion of esters to cyclopropanols[3,4] to readily transform *N*,*N*-dialkylcarboxamides to *N*,*N*-dialkylcyclopropylamines[4–6] can also be applied to prepare a variety of 2-substituted 1-aminocyclopropanecarboxylic acids[7] as well as β-amino acids containing a cyclopropane moiety.[8] However, several steps are required to transform the functional groups like C=C double bonds, ether or acetal moieties, which are compatible with the standard conditions for the preparation of Grignard reagents,[9] to a carboxylic acid. Other functionalities including ester moieties and halogen substituents are compatible with the well-examined and easily prepared organozinc reagents,[10] and thus we set out to test the possible use of various functionally substituted organozinc compounds for the reductive cyclopropanation of *N*,*N*-dialkylcarboxamides.

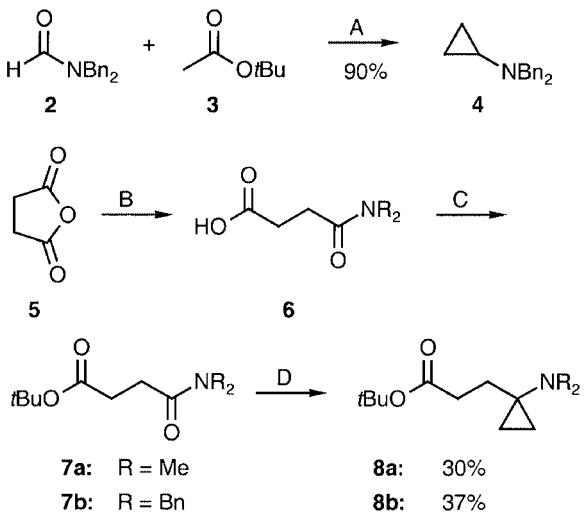


Figure

Since the titanium-mediated reductive cyclopropanation was originally developed for the conversion of esters to cyclopropanols,[2,3] the selectivity question was first addressed by some inter- as well as intramolecular competition experiments.

In fact, a 1:1 mixture of *N*,*N*-dibenzylformamide (**2**) and *tert*-butyl acetate (**3**), when treated with ethylmagnesium bromide and methyltitanium triisopropoxide,[5] yielded only *N*,*N*-dibenzylcyclopropylamine (**4**) (90%), and the *tert*-butoxycarbonyl-substituted amides **7** gave the γ-cyclopropanated γ-(dialkyl)aminobutyric esters **8** selectively, albeit in moderate yields (Scheme 1). Thus, it ought to be possible to apply functionalized organozinc compounds including those with *tert*-butyl ester functionalities in the titanium-mediated reductive cyclopropanation of amides.

However, none of the original protocols developed for the use of Grignard reagents[4–6] gave the desired aminocyclo-

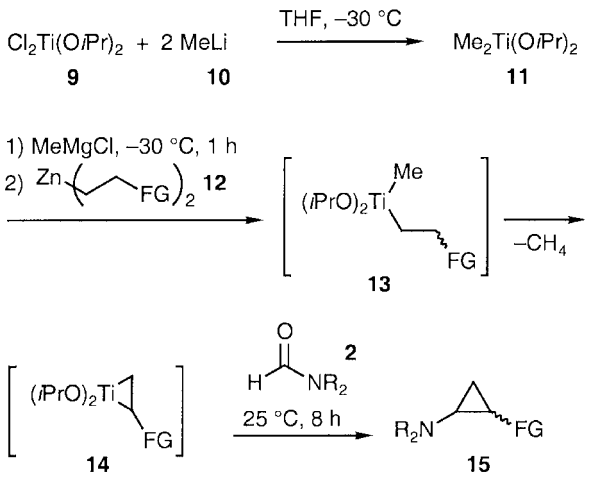


Scheme 1 A: MeTi(*i*-PrO)$_3$, EtMgBr, THF, 25 °C, 8 h. – B: R_2NH. – C: Isobutene, H_2SO_4, Et_2O, 25 °C, 24 h. – D: EtMgBr, MeTi(*i*-PrO)$_3$, THF, 25 °C, 8 h.

Synlett 2002, No. 6, 04 06 2002. Article Identifier:
1437-2096,E;2002,0,06,0879,0882,ftx,en;G05902ST.pdf.

ISSN 0936-5214

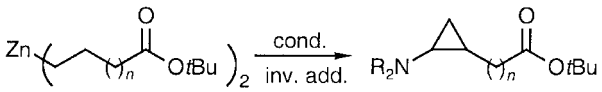
propane derivatives from *tert*-butoxycarbonyl-**16** and chloro-substituted organozinc compounds **18**.[11] Further modifications of the reaction conditions were first tested with commercially available diethylzinc which, under established conditions, gave cyclopropylamines in yields of only up to 25%.[12] However, it was found that upon addition of 2 equivalents of sodium isopropoxide, diethylzinc in tetrahydrofuran in the presence of methyltitanium triisopropoxide converted *N,N*-dialkylcarboxamides to *N,N*-dialkylcyclopropylamines in yields as high as those achieved with ethylmagnesium halides (up to 89%).[13,14] But even these conditions failed when functionalized organozinc reagents were employed. Therefore, different titanium derivatives were tested. Indeed, when the functionalized organozinc was first treated with dichlorodiisopropyloxytitanium (**9**), then after 30 minutes an excess (5 equiv) of methylmagnesium chloride was added, and finally dibenzylformamide, the (2-dibenzylaminocyclopropyl)-substituted *tert*-butyl acetate **17aa** was isolated at best in 49% yield (Table 1, conditions A). Several other functionally substituted organozinc derivatives were employed according to this protocol and gave the corresponding cyclopropylamines in moderate yields (21–61%). Most probably the dichlorodiisopropyloxytitanium partially transmetallates the functionalized organozinc, as evidenced by a change in appearance of the reaction mixture from colorless to red. This can be enhanced by the added methylmagnesium chloride which can react with the organozinc before transmetallation to form a more basic zincate, or also with the unreacted dichlorodiisopropyloxytitanium with single or twofold exchange of the chlorine substituents by methyl groups or with the first formed alkylchlorodiisopropyloxytitanium intermediate.[15] Eventually, an alkylmethyldiisopropyloxytitanium intermediate **13** will be formed which, by β-hydride transfer from the functional alkyl to the methyl group, affords the functionally substituted titanacyclopropane intermediate **14** that subsequently reacts in the same manner as the intermediate in the original reductive cyclopropanation[4] of carboxamides (Scheme 2).



Scheme 2

Another series of optimization experiments revealed that consistently and reproducibly better yields were obtained when dimethyldiisopropyloxytitanium (**11**) was prepared from dichlorodiisopropyloxytitanium (**9**) and two equivalents of methyllithium[16] prior to the addition of one equivalent of methylmagnesium chloride and the freshly prepared organozinc compound (Table 1, conditions B). The additional equivalent of methylmagnesium chloride – which turned out to be better than an additional equivalent of methyllithium – was necessary apparently to form the more reactive zincate before transmetallation and/or the more reactive titanate after transmetallation to titanium.[15]

Table 1



16 **17**

16	*n*	Cond.[a]	R,R	**17**	Yield (%)	*trans*/*cis*
a	1	A	Bn, Bn	**aa**	49	1.1:1
a	1	B	Bn, Bn	**aa**	60	1.8:1
a	1	B	Me, Me	**ab**	63	1.3:1
a	1	B	$-(CH_2)_5-$	**ac**	52	1.4:1
b	2	B	Bn, Bn	**ba**	40	1.2:1
c	3	B	Bn, Bn	**ca**	24	1.1:1

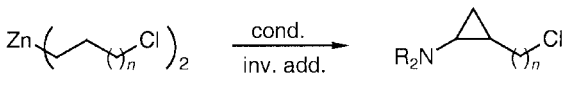
[a] A: (1) $Cl_2Ti(i\text{-}PrO)_2$, THF, –30 °C, 1 h. (2) MeMgCl (5 equiv), THF, –30 to 20 °C, 8 h; – B: (1) $Me_2Ti(i\text{-}PrO)_2$, MeMgCl; (2) R_2NCHO, THF, –30 to 25 °C, 8 h.

According to this protocol, various *tert*-butoxycarbonyl- and chloroalkyl-substituted cyclopropylamine derivatives were prepared in yields ranging from 24 to 67% (Table 1 and Table 2).[17,18]

For the *tert*-butoxycarbonyl-substituted systems, an increase in the chain length between the functional group and the metal led to decreasing yields. From bis(4-chlorobutyl)zinc, the major product was (2-ethenylcyclopropyl)dibenzylamine (31% yield) formed by subsequent dehydrochlorination in addition to 27% of the [2-(2′-chloroethyl)cyclopropyl]dibenzylamine (**19aa**).

Thus, the newly developed protocol makes various functionalized aminocyclopropanes easily accessible in virtually one operational step. These products are valuable building blocks for the synthesis of pharmacologically interesting molecules containing aminocyclopropane moieties. Further investigations are continuing towards the direct synthesis of cyclopropyl-group containing α-amino acids in one or two steps.

Table 2



18 **19**

18	*n*	Cond.[a]	R,R	**19**	Yield (%)	*trans*/*cis*
a	2	B	Bn, Bn	**aa**	27[b]	1.2:1
b	3	A	Bn, Bn	**ba**	61	1.4:1
b	3	B	Me, Me	**ba**	65	1.2:1
b	3	B	$-(CH_2)_5-$	**bb**	67	1.2:1
b	3	B	Bn, Bn	**bc**	55	1.1:1
c	4	A		**ca**	57	1.1:1
c	4	B	Bn, Bn	**ca**	61	1.1:1

[a] A: (1) $Cl_2Ti(i\text{-}PrO)_2$, THF, –30 °C, 1 h. (2) MeMgCl (5 equiv), THF, –30 to 20 °C, 8 h; – B: (1) $Me_2Ti(i\text{-}PrO)_2$, MeMgCl; (2) R_2NCHO, THF, –30 to 25 °C, 8 h. –

[b] In addition, dibenzyl(2-ethenylcyclopropyl)amine was isolated in 31% yield.

Acknowledgement

This work was supported by the Niedersächsisches Ministerium für Wissenschaft und Kunst, the Deutsche Forschungsgemeinschaft (SFB 416, Project A3), and the Fonds der Chemischen Industrie. The authors are indebted to Prof. Paul Knochel, München, for valuable discussions, and to Dr. Burkhard Knieriem, Göttingen, for his careful proofreading of the final manuscript.

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(17) All new compounds were fully characterized by spectroscopic methods (IR, ^1H and ^{13}C NMR, MS) and elemental analyses. **General Procedure B (GPB)**: To a solution of $Cl_2Ti(O\text{-}i\text{-}Pr)_2$ (1043 mg, 4.0 mmol) in THF (5 mL) kept at –30 °C, was added 5.3 mL of a 1.65 M solution of methyllithium (8.8 mmol) in hexane. Then 1.5 mL of a 3 M solution of methylmagnesium chloride (4.5 mmol) in THF was added, and the mixture was stirred for 1 h at this temperature. After that the previously prepared solution of the organozinc compound in THF and the *N*,*N*-dialkylcarboxamide (4 mmol) were added, the mixture was slowly warmed up to r.t. until gas evolution ceased, and stirred for an additional 8 h. The reaction was quenched by addition of 2 mL of H_2O, and stirring of the mixture continued until the color of the suspension had turned yellow. The mixture was filtered, and the solid was washed with diethyl ether (2 × 10 mL). The combined organic phases were dried over Na_2SO_4. The crude products were purified by column chromatography. For example **(2-Dibenzylaminocyclopropyl)acetic Acid *tert*-Butyl Ester (17aa)**: From *tert*-butyl 4-iodobutyrate and *N*,*N*-dibenzylformamide, following GPB as above, two diastereomeric products were isolated by column chromatography (70 g of silica gel, diethyl ether/pentane 1:10).
Fraction I (R_f = 0.83): 300 mg (21%) of *cis*-(2-dibenzylaminocyclopropyl)acetic acid *tert*-butyl ester (*cis*-**17aa**) as a colorless oil. IR(film): ν = 3063, 2977, 2928, 1733, 1494, 1454, 1367, 1152, 1028, 749, 698 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.13 (ddd, ^3J = 4.5, ^3J = 4.9, ^2J = 5.1 Hz, 1 H, 3′-H), 0.73 (ddd, ^2J = 5.1, ^3J = 6.9, ^3J = 8.6 Hz, 1 H, 3′-H), 1.14 (ddddd, ^3J = 4.9, ^3J = 6.8, ^3J = 7.0, ^3J = 7.2, ^3J = 8.6 Hz, 1 H, 1′-H), 1.34 [s, 9 H, $C(CH_3)_3$], 1.96 (ddd, ^3J = 4.5, ^3J = 6.9, ^3J = 7.0 Hz, 1 H, 2′-H), 2.41 (dd, ^3J = 6.8, ^2J = 16.4 Hz, 1 H, 2-H), 2.48 (dd, ^3J = 7.2, ^2J = 16.4 Hz, 1 H, 2-H), 3.50 (d, ^2J = 13.8 Hz, 2 H, C*H*HPh), 3.69 (d, ^2J = 13.8 Hz, 2 H, CH*H*Ph), 7.35–7.21 (m, 10 H, Ph-C). ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 12.1 (–, C-3′), 15.1 (+, C-1′), 28.0 [+,$OC(CH_3)_3$], 33.9 (–, C-2), 40.1 (+, C-2′), 57.5 (–, NCH_2), 80.0 [C_{quat}, $OC(CH_3)_3$], 126.8 (+, Ph-C), 128.0 (+, Ph-C), 129.4 (+, Ph-C), 138.1 (C_{quat}, Ph-C), 173.5(C_{quat}, C=O). MS (EI, 70 eV): *m/z* (%) = 351(6) [M^+], 278(9), 260(4), 236(9), 204(100), 181(2), 158(5),106(4), 91(81). Anal. Calcd for $C_{23}H_{29}NO_2$: C, 78.60; H, 8.32; N, 3.99. Found: C, 78.44; H, 8.34; N, 4.04.
Fraction II (R_f = 0.58): 542 mg (39%) of *trans*-(2-dibenzylaminocyclopropyl)acetic acid *tert*-butyl ester (*trans*-**17aa**) as a colorless oil. IR(film): ν = 3063, 3028, 2978, 2929, 1732, 1602, 1494, 1454, 1392, 1367, 1257, 1154, 1076, 1029, 955, 750, 699, 620 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.34 (ddd, ^2J = 5.3, ^3J = 5.3, ^3J = 6.7 Hz, 1 H, 3′-H), 0.61 (ddd, ^3J = 3.3, ^2J = 5.3, ^3J = 8.0 Hz, 1 H, 3′-H), 1.04 (ddddd, ^3J = 3.4, ^3J = 5.3, ^3J = 7.2, ^3J = 7.2, ^3J = 8.0 Hz, 1 H, 1′-H), 1.42 [s, 9 H, $C(CH_3)_3$], 1.68 (ddd, ^3J = 3.3, ^3J = 3.4, ^3J = 6.7 Hz, 1 H, 2′-H), 2.02 (dd, ^3J = 7.2, ^2J = 14.6 Hz, 1 H, 2-H),

2.07 (dd, ^3J = 7.2, ^2J = 14.6 Hz, 1 H, 2-H), 3.64 (d, ^2J = 13.5 Hz, 2 H, C*H*HPh), 3.71 (d, ^2J = 13.5 Hz, 2 H, CH*H*Ph), 7.35–7.22 (m, 10 H, Ph-C). ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 14.2 (–, C-3′), 17.6 (+, C-1′), 28.1 [+, $OC(CH_3)_3$], 38.6 (–, C-2), 43.1 (+, C-2′), 57.7 (–, NCH_2), 80.2 [C_{quat}, $OC(CH_3)_3$], 126.8 (+, Ph-C), 128.0 (+, Ph-C), 129.4 (+, Ph-C), 138.6 (C_{quat}, Ph-C), 172.2 (C_{quat}, C=O). MS (EI, 70 eV): *m/z* (%) = 351(6) [M^+], 294(6), 260(5), 250(14), 236(8), 204(100), 186(3), 158(6), 131(4), 106(6), 91(81). Anal. Calcd for $C_{23}H_{29}NO_2$: C, 78.60; H, 8.32; N, 3.99. Found: C, 78.81; H, 8.10; N, 3.96.

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