A New Versatile Reagent for the Synthesis of Cyclopropylamines Including 4-Azaspiro[2.n]alkanes and Bicyclo[n.1.0]alkylamines

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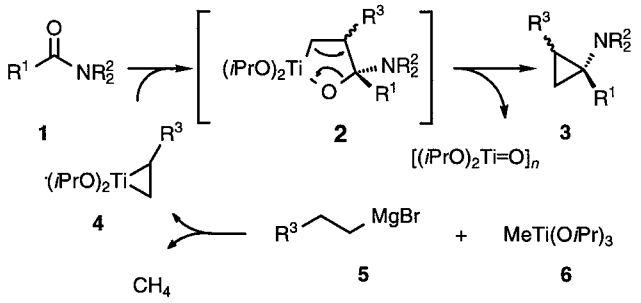
Received 21 October 1996

Abstract: The reaction of dialkylcarboxamides **1** with 1 equiv. of methyltriisopropyloxytitanium together with only 1.1 equiv. of a Grignard reagent gives cyclopropylamines **3** in better yields than the previously published method with 2 equiv. of Grignard reagent and 1 equiv. of $Ti(OiPr)_4$. This new protocol can be applied to intramolecular reactions with *in situ* generation of the Grignard reagent from ω-bromo-*N,N*-dimethylhexanamide and methyl ω-bromohexanoate yielding the expected 1-dimethylaminocyclo[4.1.0]hexane **15** and the corresponding alcohol **18**. Cyclohexylmagnesium bromide or chloride transforms *N,N*-dibenzylformamide and ethyl acetate to 7-*exo*-*N,N*-dibenzylaminonorcarane and 7-*exo*-hydroxy-7-methylnorcarane. *N*-Methyl-ε-caprolactam **25b** and even the strained N-benzylpropiolactam **25a** were converted to the spirocyclopropanated heterocycles **26a,b**.

Our adaptation of the original Kulinkovich procedure for the preparation of 1-substituted and 1,2-disubstituted cyclopropanols[1-3] has led to a convenient general synthesis of cyclopropylamines from dialkylcarboxamides and Grignard reagents mediated by tetraisopropyloxytitanium.[4] This success has further confirmed the intermediacy of a titanacyclopropane such as **4**, which can also arise by alkene exchange on a preformed titanacyclopropane.[1f,5] In conceiving an intramolecular variant of this reaction for the synthesis of bicyclic alcohols and amines we were led to think about the possibility of replacing the commonly used tetraisopropyloxytitanium or chlorotriisopropyloxytitanium with methyltriisopropyloxytitanium **6**.[6] Starting from **6** would have the advantage that only one equivalent of the Grignard reagent would be required, as one half of it would not be sacrificed as an alkane in the formation of the intermediate **4**.

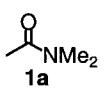
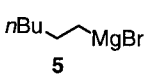
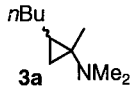
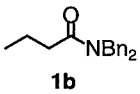
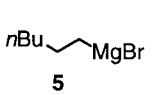
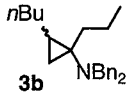
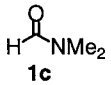
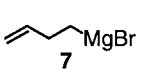
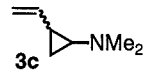
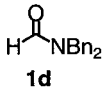
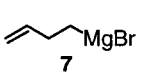
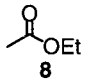
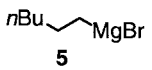
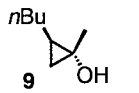
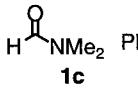
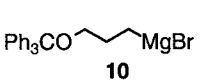
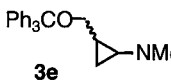
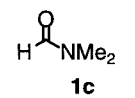
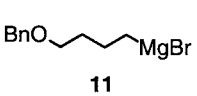
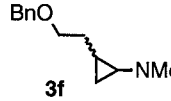
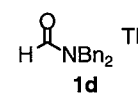
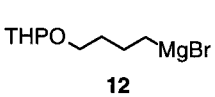
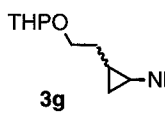
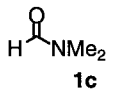
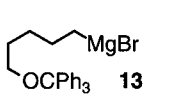
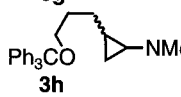


Scheme 1

This modification would make an intramolecular reductive cyclopropanation in which the Grignard reagent would be generated *in situ* from ω-bromoesters or ω-bromocarboxamides and metallic magnesium according to the Barbier procedure, more appropriate, as methane and not reductively debrominated ester or amide would be the by-product. In addition, this variant should be favorable when Grignard reagents from valuable halides need to be used to reach a synthetic target.

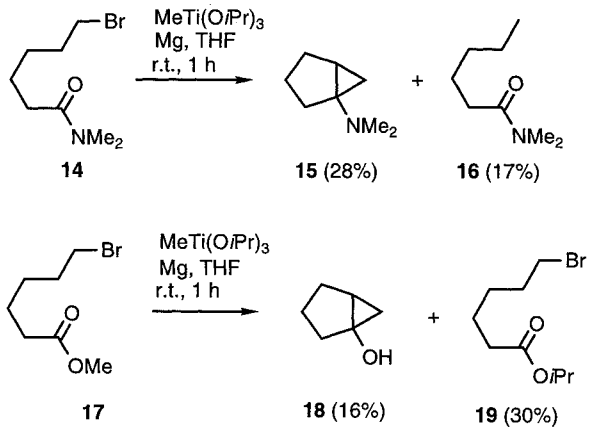
The practical execution of this idea applying 1.0 equivalent of $MeTi(OiPr)_3$ and 1.1 equivalent of a Grignard reagent (1-hexylmagnesium bromide **5** or 1-but-3-enylmagnesium bromide **7**, respectively) consistently gave better yields of cyclopropylamines **3**[7] from dialkylcarboxamides **1** and e. g. cyclopropanol **9**[7] from ethyl acetate **8** as compared to previously established[1-4] reaction conditions (Table 1). In all these cases one of the possible diastereomers (most probably the (*E*)-isomer) predominated by at least a factor of 10 : 1. Several functionalized Grignard reagents (3-triphenylmethyloxypropylmagnesium bromide **10**, 4-benzyloxybutylmagnesium bromide **11**, 4-tetrahydropyranyloxybutylmagnesium bromide **12** and 5-triphenylmethyloxypentylmagnesium bromide **13**, respectively) could also be applied under these conditions to give the corresponding cyclopropylamines **3e-h**, yet with low diastereoselectivity.

Table 1. Transformation of esters and amides to cyclopropanols and cyclopropylamines, respectively, using $MeTi(OiPr)_3$ in comparison to $Ti(OiPr)_4$.[7]

Starting Materials		Product	Yield (%) Conditions A/B[a] (d. r.)
 **1a**	 **5**	 **3a**	38 / 51[b] (>25 : 1)[c]
 **1b**	 **5**	 **3b**	35 / 47[b] (10 : 1)
 **1c**	 **7**	 **3c**	-[d] / 57 (17 : 1)[e]
 **1d**	 **7**	 **3d**	42 / 54[b] (>25 : 1)
 **8**	 **5**	 **9**	75 / 84[c]
 **1c**	 **10**	 **3e**	-[d] / 18[c] (>25 : 1)
 **1c**	 **11**	 **3f**	-[d] / 54 (1.1 : 1)
 **1d**	 **12**	 **3g**	-[d] / 34[f] (2.1 : 1)
 **1c**	 **13**	 **3h**	-[d] / 53[g] (1.8 : 1)

[a] A: **1** (1.0 equiv.), $Ti(OiPr)_4$ (1.0 equiv.), **5** (2.2 equiv.), THF, –78 °C to r.t., 5–24 h. – B: **1** (1.0 equiv.), $MeTi(OiPr)_3$ (1.0 equiv.), **5** (1.1 equiv.), THF, –78 °C to r.t., 5–15 h. – [b] Isolated yield of the main diastereomer. – [c] The second diastereomer was not detected in the ^1H NMR spectrum of the crude product. – [d] Not performed. – [e] The mixture of diastereomers was distilled, the main diastereomer had (*E*)-configuration according to a complete analysis of its ^1H NMR spectrum. – [f] Compound **1** added at +10 °C, reaction time 4 d. – [g] Compound **1** added at –10 °C, reaction time 2 d.

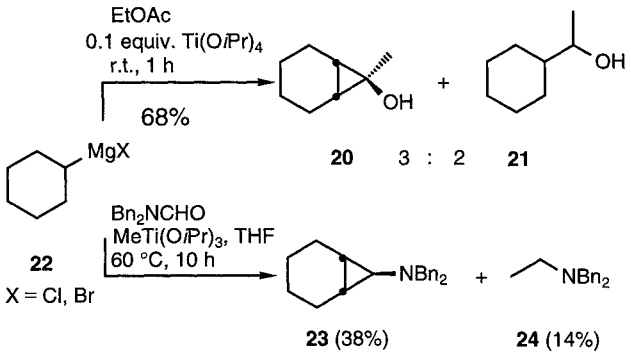
The application of this protocol to the magnesium derivatives generated *in situ* from 6-bromo-*N,N*-dimethylhexanamide and methyl 6-bromohexanoate using 2 equiv. of magnesium turnings activated with 1,2-dibromoethane and 1.1 equiv. of methyltriisopropyloxytitanium (Scheme 2) gave the expected bicyclic products **15**[8] and **18**[9] in low yield, together with by-products derived from the starting materials by reduction and transesterification, respectively.[10,11]



Scheme 2

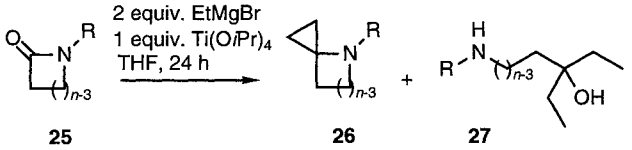
In order to probe for the scope and limitations of this reaction, the applicability of cyclic Grignard reagents such as cyclohexylmagnesium bromide and chloride as well as lactams for the construction of bi- and spirocyclic systems was tested.

Both cyclohexylmagnesium chloride and bromide[12] (ether or THF were found to be suitable solvents) afforded with ethyl acetate under the usual conditions[1] (only 0.1 equiv. of $Ti(OiPr)_4$ is needed) a 3 : 2 mixture of the expected bicyclic alcohol **20** and 1-cyclohexylethanol **21** (68% yield) which could be separated only after conversion to the corresponding silyl ethers[13] by means of preparative GC. The pure 7-methyl-7-trimethylsilyloxybicyclo[4.1.0]heptane[7] could be desilylated with methanolic citric acid[14] to yield pure 7-methylnorcarane-*exo*-7-ol **20**[7] (18% isolated yield, based on **22**). The expected *exo*-configuration was confirmed by the ^1H NMR spectrum with the triplet of cyclopropylic protons at $\delta = 0.96$ in comparison with a triplet at $\delta = 0.62$ for the *endo*-ol.[15] The analogous reaction of **22** in the presence of 1 equiv. of $MeTi(OiPr)_4$ with *N,N*-dibenzylformamide stereoselectively afforded the expected 7-*exo*-dibenzylaminobicyclo[4.1.0]hexane **23**[7] in a satisfactory yield (Scheme 3). When this reaction was performed in the previously reported way,[4] **23** was obtained in 34% yield along with dibenzyl(cyclohexylmethyl)amine (15%). The fact that the yields of both **23** and the by-products were consistently lower, when the reaction mixture was not heated, indicate a significant lifetime of the titanacyclopropane intermediate or the oxatitanacyclopentane **2** even at elevated temperature.



Scheme 3

Eventually the cyclopropanations of *N*-benzyl-β-propiolactam **25a** and *N*-methylcaprolactam **25b**[16] were studied. Indeed, when the reaction was carried out under the usual conditions[4] with both lactams, the expected spirocyclic amines **26a** and **26b**[7] were obtained with the ring-opened tertiary alcohols **27a,b** as by-products. As expected, in the presence of 1 equiv. of $MeTi(OiPr)_3$ instead of $Ti(OiPr)_4$ (using the new conditions) the same reaction led to smaller quantities of the by-product **27b** (3%) and a slightly better yield of **26b** from the lactam **25b**. It is not surprising that the formation of the by-product was dominant in the reaction of the strained β-lactam **25a**. The formation of the by-product **27a** from the latter could not be avoided, even when stoichiometric quantities of reagents were used. Conversion of **25a** was complete under such conditions, while complete conversion of **25b** was only achieved with either 4 equiv. of Grignard reagent and 2 equiv. of $Ti(OiPr)_4$ at room temperature or by employing elevated temperatures and longer reaction times with equimolar quantities of reagent.



25	*n*	R	Temp. [°C]	%	%
a	4	Bn	20	28 (21[a])	56
b	7	Me	65	44 (33[a]) 47[b]	8 3[b]

Scheme 4. [a] Isolated yield. – [b] Using 1 equiv. of $MeTi(OiPr)_3$ and 1.1 equiv. of EtMgBr.

In conclusion one can say that the use of methyltriisopropyloxytitanium instead of tetraisopropyloxytitanium for the conversion of acid dialkylamides to cyclopropylamines as well as esters to cyclopropanols represents a significant improvement over the original procedure, and is particularly favorable when a valuable or a Grignard reagent with an otherwise reactive functionality is to be applied.

Acknowledgement

This work was supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and by the companies BASF, Bayer, Degussa, and Hüls AG (chemicals). V. C. is indebted to the Gottlieb-Daimler- und Carl-Benz-Stiftung for a graduate fellowship.

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6. Prepared from methyllithium and chlorotriisopropyloxytitanium: Imwinkelried, R.; Seebach, D. *Org. Synth.* **1989**, *67*, 180.
7. All new compounds were fully characterized by spectroscopic methods (IR; ^{1}H NMR, ^{13}C NMR, MS) and their molecular formulas confirmed by elemental analysis or HRMS. Cyclopropylamines were isolated as free amines by column chromatography except the diastereomeric mixture of **3c**, which was distilled under reduced pressure (270 mm Hg). Spectroscopic data of representative examples of new compounds are as follows: **3a**: colorless oil; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.12 (dd, ^2J = 4.4, ^3J = 6.3 Hz, 1 H, 3-H), 0.42 (dd, ^2J = 4.4, ^3J = 8.5 Hz, 1 H, 3-H), 0.50–0.63 (m, 1 H, 2-H), 0.90 (t, ^3J = 7.0 Hz, 3 H, CH_3CH_2), 0.98 (s, 3 H, 1-CH_3), 1.18–1.43 [m, 5 H, $(CH_2)_3$], 1.60–1.80 (m, 1 H, CH_2), 2.29 (s, 6 H, NCH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$, additionally DEPT): δ = 13.78 (+, CH_3), 14.29 (+, CH_3), 20.87 (–, CH_2), 22.83 (–, CH_2), 27.19 (–, CH_2), 28.70 (+, C-2), 32.67 (–, CH_2), 41.33 (+, NCH_3), 43.97 (C_{quat}, C-1). – **3c**: colorless oil, bp. 72 °C (270 mm Hg); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.63 (m, 1 H, 2-H), 0.85 (m, 1 H, 2-H), 1.43 (m, 1 H), 1.52 (m, 1 H), 2.29 (s, 6 H, CH_3), 4.85 (dd, ^2J = 1.5, $^3J_{cis}$ = 9.7 Hz 1 H, ethenyl-H_B), 5.00 (dd, ^2J = 1.5, $^3J_{trans}$ = 16.4 Hz, 1 H, ethenyl-H_A), 5.42 (m, 1 H, ethenyl-H_X); ^{13}C NMR (62.9 MHz, $CDCl_3$, additionally DEPT): δ = 15.54 (–, C-3), 24.31 (+, C-2), 44.97 (+, CH_3), 48.47 (+, C-1), 112.22 (–, C-2'), 139.75 (+, C-1'). – **9**: colorless oil; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.02 (dd, ^3J = 5.9, ^2J = 4.7 Hz, 1 H, 3-H), 0.78 (dd, ^2J = 4.7, ^3J = 9.8 Hz, 1 H, 3-H), 0.82–1.00 (m, 1 H, 2-H und t, ^3J = 6.8 Hz, 3 H, CH_3CH_2), 1.02–1.20 (m, 1 H, CH_2), 1.22–1.43 [m, 8 H, 1-CH_3 and $(CH_2)_3$], 2.61–2.80 (bs, 1 H, OH); ^{13}C NMR (62.9 MHz, $CDCl_3$, additionally DEPT): δ = 14.08 (+, CH_3), 20.11 (–, CH_2), 20.47 (+, C-2), 22.53 (–, CH_2), 25.47 (+, CH_3), 29.60 (–, CH_2), 31.93 (–, CH_2), 55.44 (C_{quat}, C-1). – **3e**: colorless oil; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.34 (m_c, 1 H, 3-H), 0.63 (m_c, 1 H, 3-H), 1.16 (m_c, 1 H, 2-H), 1.43 (m_c, 1 H, 1-H), 2.40 (s, 6 H, CH_3), 2.63 (dd, ^2J = 9.6, ^3J = 8.5 Hz, 1 H, *CH*HO), 3.14 (dd, ^2J = 9.6, ^3J = 4.2 Hz, 1 H, CH*H*O), 7.18–7.47 (m, 15 H, Ph-H); ^{13}C NMR (62.9 MHz, $CDCl_3$, additionally DEPT): δ = 11.50 (–, C-3), 20.46 (+, C-2), 45.07 (+, CH_3), 45.70 (+, C-1), 65.90 (–, CH_2O), 86.10 (C_{quat}, CPh_3), 126.82 (+, C-Ph), 127.96 (+, C-Ph), 128.63 (+, C-Ph), 144.35 (C_{quat}, C-Ph); MS (DCI, NH_3), *m/z* (%): 358 (100) [M^++H], 243 (15) [Ph_3C^+]. – **3f**, 1st diastereomer: colorless oil; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.35 (m_c, 1 H, 3-H), 0.60–0.69 (m, 1 H, 3-H), 0.93 (m_c, 1 H, 2-H), 1.34 (m_c, 1 H, 1-H), 1.39–1.54 (m, 1 H, 4-H), 1.54–1.73 (m, 1 H, 4-H), 2.35 (s, 6 H, CH_3), 3.57 (m_c, 2 H, 5-H), 4.55 (s, 2 H, CH_2Ph), 7.25–7.40 (m, 5 H, Ph-H); ^{13}C NMR (62.9 MHz, $CDCl_3$, additionally DEPT): δ = 13.49 (–, C-3), 17.51 (+, C-2), 32.65 (–, C-4), 44.90 (+, CH_3), 46.72 (+, C-1), 69.97 (–, C-5), 72.84 (–, CH_2Ph), 127.35 (+, C-Ph), 127.48 (+, C-Ph), 128.20 (+, C-Ph), 138.44 (C_{quat}, C-Ph). – **3f**, 2nd diastereomer: colorless oil; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.02–0.14 (m 1 H, 3-H), 0.57–0.70 (m, 1 H, 3-H), 0.89 (m_c, 1 H, 2-H), 1.51–1.71 (m, 2 H, 1-H, 1 × 4-H), 2.05 (m_c, 1 H, 4-H), 2.32 (s, 6 H, CH_3), 3.55–3.69 (m, 2 H, 5-H), 4.57 (s, 2 H, CH_2Ph), 7.21–7.47 (m, 5 H, Ph-H); ^{13}C NMR (62.9 MHz, $CDCl_3$, additionally DEPT): δ = 11.26 (–, C-3), 15.81 (+, C-2), 27.26 (–, C-4), 44.11 (+, C-1), 45.64 (+, CH_3), 70.90 (–, C-5), 72.73 (–, CH_2Ph), 127.30 (+, C-Ph), 127.45 (+, C-Ph), 128.22 (+, C-Ph), 138.74 (C_{quat}, C-Ph). – **3g**, 1st diastereomer: colorless oil; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.04–0.10 (m, 1 H, 3-H), 0.62–0.70 (m, 1 H, 3-H), 0.85–0.96 (m, 1 H, 2-H), 1.54–2.04 (m, 9 H, 1-H, 4-H, 7-H, 8-H, 9-H), 3.44–3.58 (m, 2 H, 5-H), 3.57 (d, ^2J = 13.8 Hz, 2 H, *CH*HPh), 3.74 (d, ^2J = 13.8 Hz, 2 H, CH*H*Ph), 3.78–3.95 (m, 2 H, 10-H), 4.58–4.64 (m, 1 H, 6-H), 7.22–7.37 (m, 10 H, Ph-H); ^{13}C NMR (62.9 MHz, $CDCl_3$, additionally DEPT): δ = 12.34 (–, C-3), 16.45, 16.53 (+, C-2), 19.52, 19.73 (–, C-8), 25.45 (–, C-4), 27.46, 27.54 (–, C-9), 30.69, 30.75 (–, C-7), 40.38 (+, C-1), 57.50 (–, C-11), 62.05, 62.44 (–, C-5), 67.97, 68.28 (–, C-10), 98.52, 99.03 (+, C-6), 126.71 (+, C-Ph), 127.94 (+, C-Ph), 129.42 (+, C-Ph), 138.32 (C_{quat}, C-Ph). – **3g**, 2nd diastereomer: colorless oil; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.25–0.32 (m, 1 H, 3-H), 0.48–0.55 (m, 1 H, 3-H), 0.68–0.78 (m, 1 H, 2-H), 1.22–1.36 (ddt, ^2J = 13.7, ^3J = 6.3, ^3J = 7.4 Hz, 1 H, 4-H), 1.47–1.81 (m, 8 H, 1-H, 4-H, 7-H, 8-H, 9-H), 3.24–3.34 (m, 1 H, 5-H), 3.42–3.53 (m, 1 H, 5-H), 3.58–3.71 (m, 5 H, 10-H and CH_2Ph), 3.77–3.90 (m, 1 H, 10-H), 4.47–4.54 (m, 1 H, 6-H), 7.20–7.34 (m, 10 H, Ph-H); ^{13}C NMR (62.9 MHz, $CDCl_3$, additionally DEPT): δ = 14.04, 14.09 (–, C-3), 18.81, (+, C-2), 19.57, (–, C-8), 25.42 (–, C-4), 30.67, (–, C-9), 32.47, 32.62 (–, C-7), 43.47, 43.51 (+, C-1), 58.10, 58.23 (–, C-5), 62.24, (–, C-11), 66.78, 67.05 (–, C-10), 98.56, 98.78 (+, C-6), 126.71 (+, C-Ph), 127.92 (+, C-Ph), 129.31 (+, C-Ph), 138.73, 138.77 (C_{quat}, C-Ph). – **20**: colorless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.92–1.00 (m, 2 H, 1-H, 6-H), 1.05–1.27 (m, 4 H, 3-H, 4-H), 1.32 (s, 3 H, CH_3), 1.28-1.47 (m, 2 H, 2-H), 1.66–1.78 (m, 2 H, 5-H), 3.50 (bs, 1 H, OH); ^{13}C NMR (62.9 MHz, $CDCl_3$, additionally DEPT) δ 16.51 (+, CH_3), 18.25 (–, CH_2), 19.96 (+, C-1 and C-6), 21.32 (–, CH_2), 58.86 (C_{quat}, C-7); MS (70 eV), *m/z* (%): 126 (1) [M^+], 125 (2), 97 (7), 81 (12), 69 (28), 67 (20), 55 (24), 53 (20) 43 (100), 41 (89). – **23**: colorless solid; mp 50 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.72–0.84 (m, 2 H, 1-H, 6-H), 0.93–1.24 (m, 4 H, 3-H, 4-H), 1.40–1.58 (m, 3 H, 2-H, 7-H), 1.60–1.80 (m, 2 H, 5-H), 3.65 (s, 4 H, CH_2Ph), 7.15–7.40 (m, 10 H, Ph-H); ^{13}C NMR (62.9 MHz, $CDCl_3$, additionally DEPT) δ 19.82 (+, C-1 and C-6), 21.86 (–, CH_2), 22.96 (–, CH_2), 48.78 (+, C-7), 58.50 (–, CH_2Ph), 126.70 (+, Ph-C), 127.90 (+, Ph-C), 129.44 (+, Ph-C), 138.99 (C_{quat}, Ph-C); MS (70 eV), *m/z* (%): 291 (4) [M^+], 210 (8), 200 (72) [M^+–C_7H_7], 106 (34), 91 (100) [$C_7H_7^+$], 65 (15), 41 (7). – **26a**: colorless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.31 (m_c, 2 H, *c*Pr-H), 0.64 (m_c, 2 H, *c*Pr-H), 2.28 (t, ^3J = 7.8 Hz, 2 H, 6-H), 3.20 (t, ^3J = 7.8 Hz, 2 H, 5-H); 3.31 (s, 2 H, CH_2Ph); 7.06–7.36 (m, 5 H, Ph-H), ^{13}C NMR (62.9 MHz, $CDCl_3$, additionally DEPT): δ = 6.33 (–, *c*Pr-C), 26.71 (–, C-6), 50.83 (C_{quat}, C-3), 51.47 (–, C-5), 58.12 (–, CH_2Ph), 126.77 (+, Ph-C), 128.17 (+, Ph-C), 128.42 (+, Ph-C), 138.10 (C_{quat}, Ph-C); MS (70 eV), *m/z* (%): 173 (17) [M^+], 172 (10), 158 (16), 145 (27), 144 (31), 130 (16), 118 (17), 117 (31), 91 (100) [$C_7H_7^+$], 90 (15), 65 (18). – **26b**: colorless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.38 (m_c, 2 H, *c*Pr-H), 0.59 (m_c, 2 H, *c*Pr-H), 1.46–1.77 (m, 8 H, CH_2), 2.42 (s, 3 H, CH_3), 2.80–2.88 (m, 2 H, NCH_2); ^{13}C NMR (62.9 MHz, $CDCl_3$, additionally DEPT): δ 16.21 (–, *c*Pr-C), 25.24 (–, CH_2), 25.59 (–, CH_2), 27.38 (–, CH_2), 32.36 (–, CH_2), 38.21 (+, NCH_3), 43.64 (C_{quat}, C-3), 54.07 (–, C-9); hydrochloride: mp. 156 °C ($MeOH/Et_2O$).
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