Reactions with 4-Hydroxy-2-methylbutananilides: Unexpected Formation of a Cyclopropanecarboxamide

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The successive treatment of the *N*,*N*-disubstituted 4-hydroxy-2-methylbutanamide **2a** with lithium diisopropylamide (LDA) and diphenyl phosphorochloridate (DPPCl) led to the 1-methylcyclopropanecarboxamide **10** in good yield. This base-catalyzed cyclization offers a new approach to cyclopropanecarboxamides. Under similar conditions, the *N*-monosubstituted 4-hydroxy-2-methylbutanamide **2b** gave the 3-methylpyrrolidin-2-one **11**. The structure of the cyclopropanecarboxamide **10** was established by Xray crystallography.

Introduction. – In the last four decades, it has been demonstrated that 2,2disubstituted 2*H*-azirin-3-amines of type **1** are attractive building blocks for the introduction of 2,2-disubstituted glycines into peptides, as well as for the synthesis of heterocycles [1]. The *N*-methyl-*N*-phenyl derivatives are conveniently accessible *via* successive treatment of anilides **2** with lithium diisopropylamide (LDA), diphenyl phosphorochloridate (DPPCl), and NaN₃ [2] (*Scheme 1*). It is assumed that 1-azido



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enamines **3** are intermediates, which spontaneously cyclize *via* elimination of N_2 to give 2*H*-azirines **1**.

Two typical examples for ring-enlargement reactions with **1** are shown in *Scheme 1*. The reaction with N*H*-acidic isothiazol-3(2*H*)-one 1,1-dioxides **4** leads to eightmembered 1,2,5-thiadiazocine derivatives **5** via cleavage of the N(1)=C(3) bond of **1** [3], whereas treatment of **1** with BF₃ · OEt₂ and subsequent hydrolysis gives 2oxindoles (=2,3-dihydro-1*H*-indol-2-ones) **6** via cleavage of the N(1)–C(2) bond [4]. In the second example, a 2-allyl-substituted azirine **1** (R¹ = allyl, R² = Me) has been used for the preparation of a 3-allyloxindole **6** (R¹ = allyl, R² = Me), which was further transformed into (\pm)-desoxynoreseroline [5]²). This example demonstrates that azirines of type **1** with a functionalized side chain R¹ are of high interest for the synthesis of more complex heterocycles³).

For this reason, the synthesis of 2H-azirin-3-amines **1** with an OH group in the residue R^1 was undertaken. These attempts led to unexpected results, which are presented in this report.

Results and Discussion. – The desired precursor **2a** for the azirine synthesis was obtained by the AlCl₃-catalyzed amination of α -methyl- γ -butyrolactone **7** with *N*-methylaniline according to the protocol described in [8] (see also [7a]). The reaction proceeded smoothly, and the known **2a** [7a][8] was obtained in 84% yield as colorless crystals with a m.p. of 78–78.8°. All attempts to synthesize the 2*H*-azirin-3-amine **1a** (R¹ = HOCH₂CH₂, R² = Me) according to the method described in [2] (see *Scheme 1*) by using *ca.* 1.1 equiv. of LDA failed, and only the azido derivative **8** was isolated in 48% yield as a yellow oil (*Scheme 2*). The structure determination was based on the



²) The 3-allyloxindol 6 (R¹=allyl, R²=Me) [4a] was transformed into 3-(2-hydroxyethyl)-1,3-dimethyloxindole *via* ozonolysis and subsequent NaBH₄ reduction [6]. Subsequent treatment with SOCl₂ and NH₃ yielded 3-(2-aminoethyl)-1,3-dimethyloxindole, a precursor for the cyclization to (±)-desoxynoreseroline.

³) For the synthesis of 2*H*-azirin-3-amines with a functionalized side chain, see also [7].

analytical and the IR, ¹H- and ¹³C-NMR data. The presence of the N₃ group was evidenced by the strong IR absorptions at 2096 and 1266 cm⁻¹ for the asymmetric and symmetric stretching vibration. The base peak in the CI-MS appeared at m/z 233 ($[M+1]^+$), corresponding to the formula C₁₂H₁₆N₄O for the product.

The formation of **8** can easily be rationalized by the reaction of the alcoholate of **2a** with DPPCl to give the corresponding alkyl diphenyl phosphate **9** (see, *e.g.*, [9]), followed by an S_N^2 reaction with the azide ion.

In the next experiment, **2a** was treated with *ca*. 2.2 equiv. of LDA, followed by *ca*. 1.1 equiv. of DPPCl. Surprisingly, a new, rather unpolar product was formed (TLC), which, after chromatographic workup, was obtained as a colorless, crystalline material. On the basis of the spectroscopic and analytical data, the structure was determined as 1,*N*-dimethyl-*N*-phenylcyclopropanecarboxamide (**10**; *Scheme 2*). Finally, this structure was established by X-ray crystallography (*Fig.*).



Figure. ORTEP Plot [10] of the molecular structure of **10** (50% probability ellipsoids, arbitrary atom numbering)

A likely intermediate in the formation of 10 is the anion of 9, which undergoes cyclization to give the cyclopropane by elimination of diphenyl phosphate (*cf.* [11]).

The analogous reaction of the *N*-monosubstituted amide **2b**, which had been prepared by the reaction of **7** with 4-methoxyaniline, with *ca*. 3.3 equiv. of LDA gave, after chromatographic workup, a product with a base peak in the CI-MS at m/z 206 $([M+1]^+)$, corresponding to a molecular formula of $C_{12}H_{15}NO_2$, *i.e.*, the product of the dehydration. The ¹H- and ¹³C-NMR data clearly indicated that the product was not the expected cyclopropanecarboxamide: the NMR spectra showed signals of two different CH₂ groups (*e.g.*, $\delta(C)$ 46.8 and 27.0 ppm) and of a CH group (37.9 ppm). Whereas the IR absorption at 1685 cm⁻¹ was in agreement with the structure of lactam **11** [12] as well as with the iminolactone **11'** [13], the NMR data clearly indicated that **11** was formed (*Scheme 3*). The CH₂ signals at 46.8 (¹³C) and 3.77–3.72 (¹H) ppm are characteristic for the CH₂N group [14], whereas the CH₂O signals of **11**' would be expected at *ca*. 62 and 4.2 ppm, respectively [15][16]. The formation of **11** may be rationalized by the cyclization of intermediate **12**. Although ring closure *via* nucleophilic attack of the O-or the N-atom of the amide group is possible, it has been shown that, in the case of 4-bromobutyranilide, under very basic conditions, *i.e.*, in the cyclization of the corresponding anion, the formation of the lactam is strongly preferred [17].

Scheme 3



Ar = 4-MeO $-C_6H_4$

Finally, the transformations of the OH group of 2a to an ester moiety in 13 and to a urethane moiety in 14 were achieved *via* the reactions with acid chlorides and isocyanates, respectively, under standard conditions (*Scheme 4*).



Conclusions. – The reaction of the *N*,*N*-disubstitued 4-hydroxybutanamide **2a** with 2 equiv. of LDA and DPPCl led to the cyclopropanecarboxamide **10**, whereas the analogous *N*-monosubstituted amide **2b** under similar conditions yielded the lactam **11**. The formation of **10** *via* the base-catalyzed cyclization of **2a** offers a new access to the important class of cyclopropanecarboxamides⁴), which are known as partial structures of physiologically active compounds (*e.g.*, DPP-IV inhibitors [19a], melanocortin receptor agonists [19b], antidepressants [19c], HCV NS5B inhibitors [19d][19e], etc.). The described results show that, for the attempted synthesis of a 2*H*-azirin-3-amine **1** with an OH group in R¹, a starting material **2** with a suitably protected OH group should be used.

⁴) For recent syntheses of cyclopropanecarboxamides, see [18].

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Experimental Part

1. General. Solvents were purified by standard procedures. TLC: aluminium sheets, silica gel 60 F_{254} (Merck). Prep. TLC: glass plates, silica gel 60 F_{254} (2 mm; Merck). Column chromatography (CC): silica gel C-560 (0.04–0.063 mm; Uetikon-Chemie). Medium-pressure liquid chromatography (MPLC): LiChroprep Si 60, 15–25 µm (Merck); column: Kron-Lab 4/98-Pro, 480 × 30 mm or Labomatic, 380 × 20 mm. M.p.: Mettler-FP-5 or Büchi 510 apparatus; uncorrected. IR Spectra: Perkin-Elmer 781 or Perkin-Elmer 1600 FT-IR spectrophotometer; in KBr unless otherwise stated. ¹H- and ¹³C-NMR Spectra: Bruker ARX-300 instrument (300 and 75.5 MHz, resp.), in CDCl₃; multiplicities of C-atoms from DEPT spectra. MS: Finnigan MAT-90, Finnigan SSQ-700 (CI with NH₃), or Finnigan TSQ-700 instrument (ESI). Elemental analyses were performed by the Mikroanalytisches Laboratorium des Organisch-chemischen Instituts der Universität Zürich (Elementar Vario EL instrument).

2. *Starting Materials.* The preparation of *4-hydroxy-2*,N-*dimethyl*-N-*phenylbutanamide* (2a) was carried out according to [8] and has been previously described in [7a]. All other reagents were commercially available.

3. Reactions with 4-Hydroxy-2,N-dimethyl-N-phenylbutanamide (2a). 3.1. 4-Azido-2,N-dimethyl-Nphenylbutanamide (8). To a stirred soln. of Pr_2NH (0.47 ml, 3.32 mmol) in THF (10 ml) at -20° , BuLi (2M soln. in pentane, 1.60 ml, 3.20 mmol) was added under Ar, and the mixture was allowed to warm to 0° . A soln. of **2a** (600 mg, 2.89 mmol) in THF (5 ml) was added dropwise, and the mixture was stirred at 0° for 1 h. Then, diphenyl phorphorochloridate (DPPCl; 0.62 ml, 2.98 mmol) was added dropwise. After 30 min, the ice bath was removed, and the mixture was stirred at r.t. for 24 h. The formed precipitate was filtered off under Ar, the THF soln. was dropped into a suspension of NaN₃ (0.565 mg, 8.69 mmol) in dry DMF (1.5 ml), and the mixture was stirred at r.t. for 4 d. Then, Et₂O was added, and the mixture was filtered over a *Celite* pad, the solvent was evaporated, and the residue was dissolved in Et₂O. The soln. was washed with 5% aq. NaHCO₃ $(2 \times)$, the aq. layer was washed with Et₂O, the combined org. layers were dried (MgSO₄), the solvent was evaporated under reduced pressure, and the crude product was purified by bulb-to-bulb distillation and CC (Et₂O/hexane 2:5): 322 mg (48%) of 8. Yellow oil. IR (film): 3061w, 2971m, 2934m, 2875m, 2096s, 1654s, 1595s, 1496s, 1462s, 1426s, 1390s, 1328m, 1266s, 1173w, 1116s, 1074m, 1037m, 1001w, 916w, 775m, 750w, 701s. ¹H-NMR: 7.50-7.36, 7.23-7.19 (2m, 5 arom. H); 3.32 - 3.14 (*m*, CH₂N₃); 3.28 (*s*, MeN), 2.64 - 2.49 (*m*, CH); 2.09 - 1.93, 1.60 - 1.47 (2*m*, CH₂); 1.05 (*d*, J =6.8, Me). ¹³C-NMR: 175.6 (s, CO); 143.7 (s, 1 arom. C); 129.7, 127.9, 127.2 (3d, 5 arom. CH); 49.3, 32.9 (2t, 2 CH_2 ; 37.4 (q, MeN); 33.8 (d, CH); 18.0 (q, Me). CI-MS: 234 (14), 233 (100, $[M+1]^+$), 205 (13), 190 (11), 107 (9).

3.2. 1,N-Dimethyl-N-phenylcyclopropanecarboxamide (10). To a stirred soln. of ⁱPr₂NH (0.94 ml, 6.65 mmol) in THF (10 ml) at -20°, BuLi (2м soln. in pentane; 3.19 ml, 6.38 mmol) was added under Ar, and the mixture was allowed to warm to 0°. A soln. of 2a (600 mg, 2.89 mmol) in THF (5 ml) was added dropwise, and the mixture was stirred at 0° for 1 h. Then, DPPCl (1.23 ml, 5.96 mmol) was added dropwise. After 30 min, the ice bath was removed, and the mixture was stirred at r.t. for 24 h. The formed precipitate was filtered off under Ar, the solvent was evaporated, and Et₂O was added. The mixture was filtered over a Celite pad, the solvent was evaporated, and the residue was dissolved in Et₂O. The soln. was washed with 5% aq. NaHCO₃ ($2\times$), the aq. layer was washed with Et₂O, the combined org. layers were dried (MgSO₄), the solvent was evaporated under reduced pressure, and the crude product was purified by CC (Et₂O/hexane 1:5): 412 mg (75%) of 10. Crystallization from hexane gave colorless prisms. M.p. 77.5-78.5°. IR: 3089w, 3046w, 2969m, 2951m, 2924m, 2867w, 1637s, 1594s, 1496s, 1469m, 1434m, 1413s, 1383s, 1370s, 1311m, 1284w, 1246s, 1158w, 1118s, 1076w, 948w, 910w, 859w, 811w, 198w, 779m, 750m, 706s. ¹H-NMR: 7.45-7.35, 7.31-7.20 (2m, 5 arom. H); 3.29 (s, MeN); 1.12-1.05, 0.44-0.37 (2m, 2 CH₂); 0.92 (s, Me). ¹³C-NMR: 174.5 (s, CO); 144.5 (s, 1 arom. C); 129.1, 127.1, 126.8 (3d, 5 arom. CH); 39.0 (q, MeN); 21.9 (q, Me); 20.8 (s, C(1)); 15.5 (t, 2 CH₂). CI-MS: 191 (12), 190 (100, [M+1]⁺). Anal. calc. for C₁₂H₁₅NO (189.25): C 76.16, H 7.99, N 7.40; found: C 76.14, H 7.85, N 7.44.

Crystals suitable for the X-ray crystal-structure determination were grown from hexane by slow evaporation of the solvent.

4. Reaction with 4-Hydroxy-N-(4-methoxyphenyl)-2-methylbutanamide (2b). 4.1. Preparation of 2b. In analogy to [8], a soln. of 4-methoxyaniline (1.54 g, 12.51 mmol) in 1,2-dichloroethane (4.5 ml) was added to a stirred suspension of AlCl₃ (0.87 g, 6.50 mmol) in 1,2-dichloroethane (2.5 ml) at 15-25°. Then, α -methyl- γ -butyrolactone (7; 0.5 ml, 5.28 mmol) was added, and the mixture was stirred at r.t. for 4 h. After quenching the reaction with ice/H₂O (5 ml), the mixture was stirred for an additional 0.5 h, the resulting suspension was filtered over Celite, and the org. phase was separated. The aq. phase was extracted with CH₂Cl₂, and the combined org. phase was washed with H₂O and brine, and dried (Na₂SO₄). Evaporation of the solvent and CC (CH₂Cl₂/MeOH 100:1) yielded 575 mg (52%) of **2b**. Pale rosa powder. M.p. 95.2-95.7°. IR: 3443m, 3283s, 3193m, 3133m, 3071w, 2974m, 2953m, 2934m, 2837m, 1652s, 1603s, 1549s, 1514s, 1459m, 1444m, 1415m, 1380m, 1348m, 1298s, 1239s, 1185m, 1170m, 1134w, 1098m, 1053s, 1035s, 1000m, 944w, 828s, 807w, 762w, 716m. ¹H-NMR: 7.88 (br. s, NH); 7.37, 6.79 (AA'BB', 4 arom. H); 3.75 (s, MeO); 3.71-3.64 (m, CH₂O); 2.87 (br. s, OH); 2.68-2.54 (m, CH); 1.97-1.84, 1.76-1.62 (2m, CH₂); 1.22 (d, J=6.9, Me). ¹³C-NMR: 175.0 (s, CO); 156.3, 130.9 (2s, 2 arom. C); 121.9, 114.0 (2d, 4 arom. CH); 60.1, 36.5 (2t, 2 CH₂); 55.4 (q, MeO); 38.5 (d, CH); 17.6 (q, Me). CI-MS: 225 (12), 224 (100, [M+1]⁺), 207 (9), 206 (77). Anal. calc. for C₁₂H₁₇NO₃ (223.27): C 64.55, H 7.67, N 6.27; found: C 64.53, H 7.85, N 6.15.

4.2. *1*-(*4-Methoxyphenyl*)-*3-methylpyrrolidin-2-one* (**11**). To a stirred soln. of ${}^{1}\text{Pr}_{2}\text{NH}$ (0.66 ml, 4.66 mmol) in THF (20 ml) at -20° , BuLi (2M soln. in pentane; 2.20 ml, 4.44 mmol) was added under Ar, and the mixture was allowed to warm to 0° . A soln. of **2b** (300 mg, 1.34 mmol) in THF (5 ml) was added dropwise, and the mixture was stirred at 0° for 1 h. Then, DPPCl (0.86 ml, 4.13 mmol) was added dropwise. After 30 min, the ice bath was removed, and the mixture was stirred at r.t. for 24 h. The mixture was worked up as described in *Sect. 3.2*, and the crude product was purified by CC (Et₂O/hexane 1:2): 240 mg (87%) of **11**. Colorless crystals. M.p. 83.1–84.8°. IR: 2952*m*, 2836*w*, 1685*s*, 1515*s*, 1482*m*, 1442*m*, 1397*s*, 1324*m*, 1290*m*, 1252*s*, 1226*s*, 1180*m*, 1121*m*, 1098*m*, 1050*m*, 1030*s*, 918*w*, 884*w*, 830*s*, 790*w*, 720*w*, 704*w*. ¹H-NMR: 7.53, 6.90 (*AA'BB'*, 4 arom. H); 3.81 (*s*, MeO); 3.77–3.72 (*m*, CH₂O); 2.73–2.59 (*m*, CH); 2.43–2.30, 1.83–1.70 (2*m*, CH₂); 1.30 (*d*, *J* = 6.7, Me). ¹³C-NMR: 176.2 (*s*, O–C=N); 156.3, 132.9 (2*s*, 2 arom. C); 121.4, 113.9 (2*d*, 4 arom. CH); 55.4 (*q*, MeO); 46.8, 27.0 (2*t*, 2 CH₂); 37.9 (*d*, CH); 16.2 (*q*, Me). CI-MS: 411 (9, [2*M*+1]⁺), 223 (8, [*M*+NH₄]⁺), 207 (13), 206 (100, [*M*+1]⁺). Anal. calc. for C₁₂H₁₅NO₂ (205.25): C 70.22, H 7.37, N 6.82; found: C 70.10, H 7.65, N 6.92.

5. Reaction of **2a** with Acid Chlorides. General Procedure 1 (GP 1). To a soln. of **2a** in dioxane, the corresponding acid chloride and Et_3N were added, and the mixture was heated to reflux for 2 h. The solvent was evaporated, and CH_2Cl_2 was added, the org. phase was washed with 10% aq. HCl, sat. aq. NaHCO₃, and brine, and dried (Na₂SO₄). After filtration, the solvent was evaporated under reduced pressure, and pure product was obtained after CC.

5.1. 3-Methyl-4-[methyl(phenyl)amino]-4-oxobutyl Acetate (13a). According to GP 1, with 2a (100 mg, 0.48 mmol), dioxane (5 ml), AcCl (0.04 ml, 0.56 mmol), and Et₃N (0.05 ml, 0.36 mmol). Yield: 108 mg (90%) of 13a. Colorless, viscous oil, which solidified on cooling. IR: 3062w, 3039w, 2970m, 2937m, 2878m, 1745s, 1650s, 1596s, 1497s, 1463m, 1429s, 1391s, 1365m, 1329m, 1244s, 1118s, 1074m, 1039s, 776s, 703s. ¹H-NMR: 7.38–7.22, 7.13–7.07 (2m, 5 arom. H); 3.89 (t, J = 6.2, CH₂O); 3.18 (s, MeN); 2.53–2.40, 2.02–1.89, 1.55–1.42 (3m, CH, CH₂); 1.83 (s, MeCO); 0.98 (d, J = 6.8, Me). ¹³C-NMR: 174.8 (s, O–C=O); 169.8 (s, CO); 143.0 (s, 1 arom. C); 128.8, 126.8, 126.4 (3d, 5 arom. CH); 61.5 (t, CH₂O) 36.4 (q, MeN); 32.3 (d, CH); 32.1 (t, CH₂); 19.8 (q, MeCO); 17.1 (q, Me). CI-MS: 516 (54, [2M + NH₄]⁺), 499 (21, [2M + 1]⁺), 267 (33, [M + NH₄]⁺), 251 (15), 250 (100, [M + 1]⁺), 249 (13, M⁺), 190 (24).

5.2. 3-Methyl-4-[methyl(phenyl)amino]-4-oxobutyl Dichloroacetate (13b). According to GP 1, with 2a (150 mg, 0.72 mmol), dioxane (10 ml), dichloroacetyl chloride (0.11 ml, 1.14 mmol), and Et₃N (0.1 ml, 0.72 mmol). Yield: 200 mg (87%) of 13b. Yellowish, viscous oil. ¹H-NMR: 7.39–7.25, 7.16–7.09 (2m, 5 arom. H); 5.73 (s, CHCl₂); 4.20–4.03 (m, CH₂O); 3.19 (s, MeN); 2.58–2.45, 2.11–1.98, 1.64–1.50 (3m, CH, CH₂); 0.98 (d, J = 6.8, Me). ¹³C-NMR: 175.2 (s, O–C=O); 164.2 (s, CO); 143.7 (s, 1 arom. C); 129.8, 127.8, 127.2 (3d, 5 arom. CH); 65.6 (t, CH₂O); 64.1 (s, CHCl₂); 37.4 (q, MeN); 33.0 (d, CH); 32.5 (t, CH₂); 18.0 (q, Me). CI-MS: 335 (17, [$M + NH_4$]⁺), 318 (100, [M + 1]⁺), 284 (19), 228 (21), 226 (64). Anal. calc. for C₁₄H₁₇Cl₂NO₃ (318.20): C 52.84, H 5.39, N 4.40, Cl 22.28; found: C 53.10, H 5.32, N 4.42, Cl 21.94.

5.3. 3-Methyl-4-[methyl(phenyl)amino]-4-oxobutyl Cyclopropanecarboxylate (13c). According to GP 1, with 2a (100 mg, 0.48 mmol), dioxane (10 ml), cyclopropanecarboxyl chloride (0.04 ml, 0.44 mmol), and Et₃N (0.07 ml, 0.50 mmol). Yield: 127 mg (95%) of 13c. Pale yellow oil. IR (film): 3061w, 3014w, 2968m, 2935m, 1719s, 1654s, 1595s, 1496s, 1454s, 1390s, 1366s, 1328m, 1270s, 1199s, 1178s, 1117s, 1074m, 1034m, 1000w, 938w, 913w, 853w, 824w, 775m, 747w, 702s. ¹H-NMR: 7.38 – 7.21, 7.11 – 7.07 (2m, 5 arom. H); 3.88 (t, J = 6.2, CH₂O); 3.17 (s, MeN); 2.53 – 2.40, 2.02 – 1.90, 1.54 – 1.42, 1.41 – 1.32 (4m, 2 CH, CH₂); 0.98 (d, J = 6.8, Me); 0.89 – 0.79, 0.78 – 0.69 (2m, 2 CH₂). ¹³C-NMR: 175.7 (s, O–C=O); 174.5 (s, CO); 143.9 (s, 1 arom. C); 129.6, 127.7, 127.2 (3d, 5 arom. CH); 62.5 (t, CH₂O); 37.3 (q, MeN); 33.2 (d, CH); 33.1 (t, CH₂); 12.7 (d, CH); 8.2, 8.1 (2t, 2 CH₂). CI-MS: 277 (16), 276 (100, [M + 1]⁺), 190 (11).

5.4. 3-Methyl-4-[methyl(phenyl)amino]-4-oxobutyl Benzoate (13d). According to GP 1, with 2a (300 mg, 1.45 mmol), dioxane (20 ml), BzCl (0.17 ml, 1.45 mmol), and Et₃N (0.2 ml, 1.43 mmol). Yield: 370 mg (82%) of 13d. Colorless, viscous oil, which solidified in h.v. IR (film): 3062w, 2970m, 1716s, 1654s, 1596s, 1496s, 1452s, 1428m, 1391s, 1315m, 1274s, 1176m, 1117s, 1071m, 1028m, 1001w, 950w, 846w, 775m, 749w, 713s. ¹H-NMR: 7.85 - 7.80, 7.50 - 7.45, 7.35 - 7.30, 7.10 - 7.00 (4m, 10 arom. H); 4.18 (br. s, CH₂O); 3.18 (br. s, MeN); 2.65 - 2.60, 2.20 - 2.10, 1.70 - 1.60 (3m, CH, CH₂); 1.04 (br. s, Me). ¹³C-NMR: 175.6 (s, O-C=O); 166.2 (s, CO); 143.8, 135.5 (2s, 2 arom. C); 132.7, 129.6, 129.4, 128.1, 127.5, 127.1 (6d, 10 arom. CH); 62.9 (t, CH₂O) 37.2 (q, MeN); 33.3 (d, CH); 33.1 (t, CH₂); 18.1 (q, Me). CI-MS: 329 (7, $[M + NH_4]^+$), 313 (18), 312 (100, $[M + 1]^+$), 190 (5), 178 (19). Anal. calc. for $C_{19}H_{21}NO_3$ (311.37): C 73.29, H 6.80, N 4.50; found: C 73.04, H 6.69, N 4.50.

5.5. 3-Methyl-4-[methyl(phenyl)amino]-4-oxobutyl 4-Nitrobenzoate (**13e**). According to *GP* 1, with **2a** (150 mg, 0.72 mmol), dioxane (10 ml), 4-nitrobenzoyl chloride (134 mg, 0.72 mmol), and Et₃N (0.1 ml, 0.72 mmol). Yield: 128 mg (50%) of **13e**. Pale yellow solid. M.p. 98.5–99.0°. IR: 3115*w*, 2970*w*, 2934*w*, 1724*s*, 1651*s*, 1610*m*, 1594*m*, 1527*s*, 1516*s*, 1496*m*, 1458*m*, 1427*m*, 1394*m*, 1350*m*, 1324*m*, 1280*s*, 1154*w*, 1122*s*, 1106*m*, 1080*w*, 1021*m*, 948*w*, 874*w*, 848*w*, 819*w*, 777*w*, 746*w*, 719*s*, 705*m*. ¹H-NMR: 8.17, 7.97 (*AA*'*BB*', 4 arom. H); 7.27–7.13, 7.10–7.04 (2*m*, 5 arom. H); 4.22 (*t*-like, CH₂O); 3.18 (*s*, MeN); 2.68–2.53, 2.25–2.08, 1.73–1.61 (3*m*, CH, CH₂); 1.05 (*d*, *J* = 6.8, Me). ¹³C-NMR: 175.5 (*s*, O–C=O); 164.3 (*s*, CO); 150.4, 143.9, 135.4 (3*s*, 3 arom. C); 130.6, 129.7, 127.7, 127.1, 123.3 (5*d*, 9 arom. CH); 64.0 (*t*, CH₂O) 37.4 (*q*, MeN); 33.4 (*d*, CH); 32.9 (*t*, CH₂); 18.1 (*q*, Me). CI-MS: 358 (19), 357 (100, [*M*+1]⁺), 328 (7), 327 (37), 240 (17), 223 (43). Anal. calc. for C₁₉H₂₀N₂O₅ (356.38): C 64.04, H 5.66, N 7.86; found: C 63.88, H 5.76, N 7.93.

6. Reaction of **2a** with Isocyanates. General Procedure 2 (GP 2). To a soln. of **2a** in dry benzene, the corresponding isocyanate was added, and the mixture was heated to reflux for 4 h. The solvent was evaporated, and the crude product was purified by CC.

6.1. 3-Methyl-4-[methyl(phenyl)amino]-4-oxobutyl (tert-Butyl)carbamate (**14a**). According to *GP* 2, with **2a** (100 mg, 0.48 mmol), benzene (10 ml), t-BuNCO (0.06 ml, 0.51 mmol). Yield: 100 mg (68%) of **14a**. Colorless, viscous oil. IR (CHCl₃): 3441w, 3007m, 2970m, 2874w, 1719s, 1641s, 1596m, 1508s, 1498s, 1457m, 1431m, 1092m, 1038w, 1001w, 921w, 839w. ¹H-NMR: 7.69–7.54, 7.44–7.38 (2m, 5 arom. H); 4.70 (br. s, NH); 4.22–4.05 (m, CH₂O); 3.49 (s, MeN); 2.82–2.69, 2.32–2.17, 1.85–1.70 (3m, CH, CH₂); 1.52 (s, 3 Me); 1.29 (d, J = 6.8, Me). ¹³C-NMR: 175.8 (s, CO); 154.7 (s, O–C(O)–N); 144.0 (s, 1 arom. C); 129.6, 127.6, 127.3 (3d, 5 arom. CH); 62.1 (t, CH₂O); 50.0 (s, Me₃C); 37.3 (q, MeN); 33.4 (t, CH₂); 33.3 (d, CH); 28.8 (q, Me₃C); 18.0 (q, Me). ESI-MS: 329 (27, $[M + Na]^+$), 307 (85, $[M + 1]^+$), 208 (47), 190 (100).

6.2. 3-Methyl-4-[methyl(phenyl)amino]-4-oxobutyl Cyclohexylcarbamate (14b). According to GP 2, with 2a (150 mg, 0.72 mmol), benzene (20 ml), cyclohexyl isocyanate (0.095 ml, 0.75 mmol). Yield: 175 mg (73%) of 14b. Colorless, viscous oil. IR (CHCl₃): 3445w, 3023s, 2977s, 2896m, 1709s, 1642m, 1590m, 1521s, 1477m, 1424s, 1047s, 929s, 877m, 850s. ¹H-NMR: 7.48 – 7.32, 7.25 – 7.17 (2m, 5 arom. H); 4.49 (br. d, NH); 4.03 – 3.88 (m, CH₂O); 3.27 (s, MeN); 2.62 – 2.45 (m, CH); 2.08 – 1.10 (m, CH₂, 11 H of cyclohexyl); 1.05 (d, J = 6.8, Me). ¹³C-NMR: 175.8 (s, CO); 155.5 (s, O–C(O)–N); 144.0 (s, 1 arom. C); 129.6, 127.6, 127.3 (3d, 5 arom. CH); 62.6 (t, CH₂O); 49.6 (d, CH of cyclohexyl); 37.3 (q, MeN); 33.4 (t, CH₂); 33.2 (d, CH); 33.3, 25.3, 24.6 (3t, 5 CH₂ of cyclohexyl); 18.0 (q, Me). ESI-MS: 371 (9, $[M + K]^+$), 356 (13), 355 (100, $[M + Na]^+$), 333 (10, $[M + 1]^+$), 190 (11), 156 (8).

6.3. 3-Methyl-4-[methyl(phenyl)amino]-4-oxobutyl Phenylcarbamate (14c). According to GP 2, with 2a (150 mg, 0.72 mmol), benzene (20 ml), PhNCO (0.08 ml, 0.72 mmol). Yield: 161 mg (68%) of 14c. Colorless, viscous oil. IR (CHCl₃): 3436w, 3023s, 2977s, 2896m, 1732s, 1642m, 1597m, 1521s, 1477m, 1424s,

1047*s*, 929*s*, 877*m*, 850*s*. ¹H-NMR: 7.52–7.30, 7.27–7.20, 7.17–7.08 (3*m*, 10 arom. H); 5.20 (br. *s*, NH); 4.20–4.02 (*m*, CH₂O); 3.30 (*s*, MeN); 2.70–2.56, 2.22–2.07, 1.72–1.59 (3*m*, CH, CH₂); 1.13 (*d*, J = 6.8, Me). ¹³C-NMR: 175.8 (*s*, CO); 153.4 (*s*, O–C(O)–N); 143.8, 138.1 (2*s*, 2 arom. C); 129.7, 128.8, 127.7, 127.2, 123.1, 118.4 (6*d*, 10 arom. CH); 63.1 (*t*, CH₂O); 37.3 (*q*, MeN); 33.4 (*t*, CH₂); 33.2 (*d*, CH); 18.1 (*q*, Me). CI-MS: 328 (20), 327 (100, [M + 1]⁺), 208 (11), 191 (10), 190 (81).

7. X-Ray Crystal-Structure Determination of **10** (Table and Fig.)⁵). All measurements were performed on a Rigaku AFC5R diffractometer using graphite-monochromated MoK_a radiation (λ 0.71069 Å) and a 12-kW rotating anode generator. The data collection and refinement parameters are given in the Table, and a view of the molecule is shown in the Figure. The intensities were corrected for Lorentz and polarization effects, but not for absorption. The structure was solved by direct methods using SHELXS97 [20], which revealed the positions of all non-H-atoms. The non-H-atoms were refined anisotropically. All of the H-atoms were fixed in geometrically calculated positions (d(C-H) = 0.95 Å), and each was assigned a fixed isotropic displacement parameter with a value equal to 1.2 U_{eq} of its parent

Crystallized from	hexane
Empirical formula	C ₁₂ H ₁₅ NO
Formula weight	189.26
Crystal color, habit	colorless, prism
Crystal dimensions [mm]	0.28 $ imes$ 0.48 $ imes$ 0.48
Temp. [K]	173(1)
Crystal system	orthorhombic
Space group	Pbca
Z	8
Reflections for cell determination	25
2θ Range for cell determination [°]	34-40
Unit cell parameters	
a [Å]	20.820(2)
<i>b</i> [Å]	14.230(3)
<i>c</i> [Å]	7.055(2)
$V[Å^3]$	2090.2(6)
D_x [g cm ⁻³]	1.203
$\mu(MoK_a) [mm^{-1}]$	0.0763
Scan type	$\omega/2\theta$
$2\theta_{(\max)}$ [°]	55
Total reflections measured	3338
Symmetry independent reflections	2391
Reflections used $[I > 2\sigma(I)]$	1671
Parameters refined	128
Final R	0.0445
wR	0.0403
Weights: <i>p</i> in $w = [\sigma^2(F_o) + (pF_o)^2]^{-1}$	0.005
Goodness of fit	1.879
Secondary extinction coefficient	$2.0(1) imes 10^{-6}$
Final $\Delta_{\rm max}/\sigma$	0.0003
$\Delta \rho (\max; \min) [e Å^{-3}]$	0.24; -0.19

Table. Crystallographic Data for Compound 10

5) CCDC-794912 contains the supplementary crystallographic data for this article. These data can be obtained free of charge from the *Cambridge Crystallographic Data Centre via* http://www.ccdc.cam.ac.uk/data_request/cif. C-atom. Refinement of the structure was carried out on *F* using full-matrix least-squares procedures, which minimized the function $\Sigma w(|F_o| - |F_c|)^2$. A correction for secondary extinction was applied. Neutral atom scattering factors for non-H-atoms were taken from [21a], and the scattering factors for H-atoms were taken from [22]. Anomalous dispersion effects were included in F_c [23]; the values for f' and f'' were those of [21b]. The values of the mass attenuation coefficients are those of [21c]. All calculations were performed using the teXsan [24] crystallographic software package.

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