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Direct Amidoalkylation of Ketones

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DIRECT AMIDOALKYLATION OF KETONES

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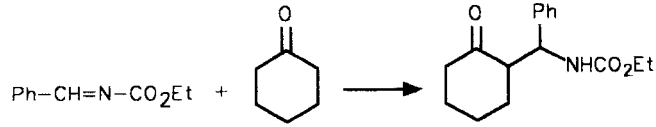
ABSTRACT: In a one-pot reaction aromatic aldehydes, urethane or acetamide and a variety of ketones condense in the presence of catalytic amounts of boron trifluoride or p-toluenesulfonic acid to furnish substituted carbamates or amides in good yield.

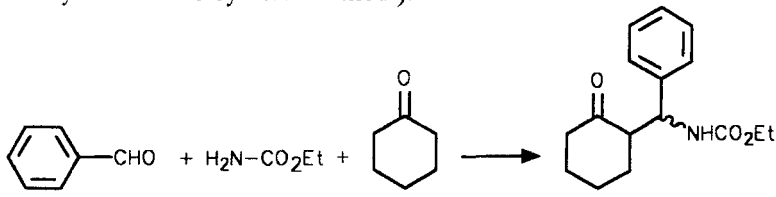
Amidoalkylation of olefins has proved to be a versatile process, especially for the construction of otherwise difficultly accessible structures[1,2]. Usually, preformed iminium salts as one reactant and aromatics or olefins (and silyl enol ethers) as the other reactant have been used. Only in a few special cases has the direct amidoalkylation of ketones been reported. For instance, Bobovski and Shavel[3] reported the acid-catalyzed reaction of ketones with a stabilized α-hydroxy-carbamate, while Khenkina and Mochalin[4] reported that the reaction of the imine **1** with cyclohexanone in the presence of boron trifluoride gives the α-amidoalkylated ketone **2**.

Because imine **1** in protonated form is generally assumed to be an intermediate in the acid-catalyzed reaction of benzaldehyde and urethane in the amidoalkylation of olefins[1], we reasoned that a mixture of benzaldehyde, urethane and cyclohexanone should also give **2** under boron trifluoride



1 2

catalysis. This assumption proved to be valid: heating a mixture of benzaldehyde, urethane and cyclohexanone in a 1:1:1 molar ratio readily gave ketone **2** as a mixture of two isomers (whereas Khenkina and Mochalin isolated only one isomer by their method[4]).



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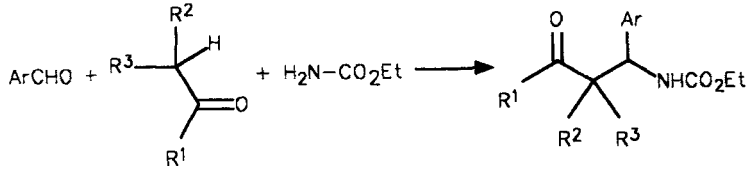
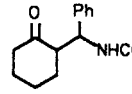
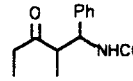
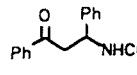
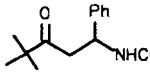
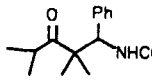
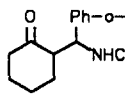
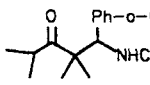
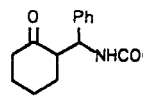
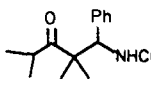
Applying this methodology to other ketones and aromatic aldehydes similarly gave the expected α-amidoalkylated ketones in fair to good yields (see Table):



Instead of boron trifluoride it appeared that a catalytic amount of p-toluenesulfonic acid could equally well be used, although generally somewhat higher temperatures were necessary. Also, urethane could be substituted for the less reactive acetamide, however, higher temperatures were usually necessary when compared to urethane.

TABLE

ENTRY	PRODUCT (a)		CONDITIONS (b)	MELTING POINT (c)
1		(70, 1/1)	A, 2d, CH_2Cl_2, RT	1) 152.5 – 154 2) 116.5 – 118.5
2		(70, 1/1)	A, 5d, CH_2Cl_2	1) 133.5 – 134.5 2) 90 – 96
3		(39)	B, 2d, CH_2Cl_2	98 – 99
4		(19)	B, 4d, $CHCl_3$	58.5 – 61
5		(73)	C, 3d, benzene	89.5 – 90
6		(66, 2/1)	A, 1d, CH_2Cl_2	1) 133.5 – 135 2) 107 – 113
7		(70)	C, 2d, toluene	76.5 – 78
8		(59, 4/1) (d)	C, 6h, toluene	158.5 – 159.5
9		(76)	C, 3d, toluene	123 – 126.5

a: Yield and isomer ratio (determined by ^{1}H-NMR) are shown in parentheses.

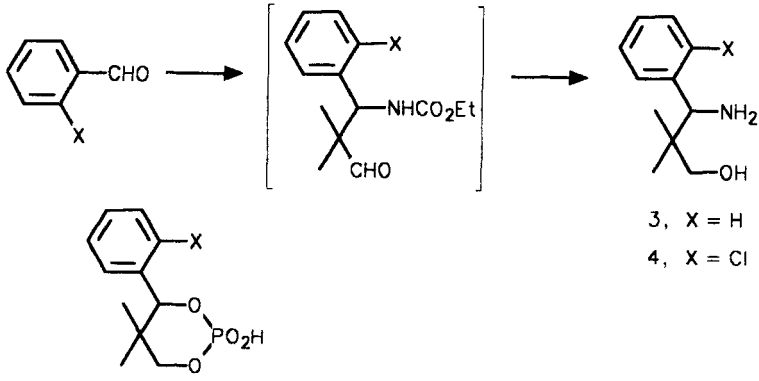
b: Procedure used, reaction time, solvent. Unless stated otherwise the reactions were run at reflux temperatures.

c: All compounds from the Table were characterized by ^{1}H-NMR spectroscopy and elemental analyses (deviation from calculated values: C, ± 0.30 (+0.42 for isomer 2 of entry 6); H, ± 0.18; N, ± 0.07 (+ 0.22 for entry 4); Cl, ± 0.20. In all cases the mp of the major isomer is shown first.

d: Minor isomer was not isolated.

Where possible, all reactions gave a mixture of the two possible diastereoisomers which were separated by crystallization; however, the more soluble isomer could not always be obtained completely free of the less soluble isomer. Remarkably, the acetamide reaction with cyclohexanone and benzaldehyde gave a higher diastereoselectivity than the corresponding urethane reaction (entry 1 vs. 8).

Our amidoalkylation is not limited to ketones but can be extended to certain aldehydes, e.g. benzaldehyde, isobutyraldehyde, and urethane in the presence of p-toluenesulfonic acid when heated in an inert solvent with azeotropic removal of water gives an intermediate aldehyde which is not purified but directly reduced with sodium borohydride in ethanol followed by hydrolysis with base to the aminoalcohol **3** in 60% overall yield[5]. Similarly, 2-chlorobenzaldehyde was transformed to the aminoalcohol **4** in 69% overall yield. Here again, acetamide could be substituted for urethane. Interestingly, aminoalcohol **3** is readily resolved using the cyclic phosphoric acid **5** (chlocyphos), whereas **4** is readily resolved using the cyclic phosphoric acid **6** (phencyphos)[6]. Substituting (-)-menthylcarbamate[7] for urethane in the two reactions mentioned above, followed by reduction and hydrolysis, led to **3** and **4** with less than 10 % enantiomeric excess.



3, X = H

4, X = Cl

5, X = Cl

6, X = H

Experimental section

Typical procedures are as follows:

Procedure A (entry 2): A mixture of 3.56 g urethane, 3.50 g 3-pentanone, 4.30 g benzaldehyde, 40 mL dichloromethane and 0.8 mL boron trifluoride etherate was heated under reflux for 5 days. The solution was washed with a sodium hydroxide solution and with water, then dried and evaporated. The residue was recrystallized from ether to give 3.98 g of product (one isomer by ^{1}H-NMR). The evaporated filtrate was purified by bulb-to-bulb distillation (140°C/0.1 mm Hg), the distillate was recrystallized from hexane to give 3.40 g of product (one isomer by ^{1}H-NMR, more soluble isomer). Total yield: 7.38 g (28.1 mmol, 70%).

Procedure B (entry 4): A mixture of 7.2 g urethane, 4.3 g benzaldehyde, 40 mL chloroform and 0.8 mL boron trifluoride etherate was stirred for 20 h at rt, then 4.2 g pinacolone was added and the mixture was heated under reflux for 4 days. After workup the residue was purified by bulb-to-bulb distillation. The fraction with bp 140-160°C/0.1 mm Hg was recrystallized from hexane/ether to give 2.10 g of pure product (7.6 mmol, 19%).

Procedure C (entry 5): A mixture of diisopropylketone, benzaldehyde, urethane (0.1 mol each), 0.8 g p-toluenesulfonic acid and 75 mL benzene was heated under reflux for 3 days with azeotropic removal of water. After workup the residue was recrystallized from hexane to give 18.58 g of colourless product. Bulb-to-bulb distillation of the evaporated filtrate (160°C/0.1 mm Hg) gave a distillate, which on recrystallization from hexane gave another 2.56 g of product, for a total yield of 21.14 g (72.6 mmol, 73%).

γ-amino, ß,ß-dimethylbenzenepropanol 3

A mixture of isobutyraldehyde (45.5 g, 0.632 mol), benzaldehyde (65 g, 0.613 mol), urethane (54 g, 0.607 mol), 1 g p-toluenesulfonic acid and 250 mL ligroin (bp 40-60°C) is heated under reflux with azeotropic removal of water for 3 h. After cooling, the mixture is poured in dilute sodium hydroxide

solution and extracted with toluene. The toluene layer is washed with water, then dried and evaporated. The residue is dissolved in 400 mL ethanol and sodium borohydride (11.3 g, 0.297 mol) in 150 mL water is added over 45 m with ice-cooling (t below 10°C). After stirring overnight at rt there is added potassium hydroxide (85 g, 1.29 mol) and the mixture is heated under reflux for 6 h. Most of the ethanol is removed by rotary evaporation, the residue is acidified with hydrochloric acid and the mixture is then extracted with toluene. The aqueous layer is basified and the product is extracted with dichloromethane. Drying, evaporation and bulb-to-bulb distillation affords 64.8 g **3** (0.362 mol, 60%) with bp 125/0.2 mm Hg as a slowly solidifying oil. ^{1}H-NMR (CCl_4): 0.7 (s, 3H), 0.9 (s, 3H), 2.7 (bs, 3H), 3.0-3.5 (AB, 2H), 3.8 (s, 1H), 7.2 (s, 5H).

Similarly, the 2-chlorophenyl analogue **4** is obtained in 69% yield as an oil after bulb-to-bulb distillation (bp 160°C/0.3 mm Hg). ^{1}H-NMR ($CDCl_3$): 0.8 (s) and 0.9 (s) (6H), 3.0 (bs, 3H), 3.3-3.6 (AB, 2H), 4.6 (s, 1H), 6.8-7.6 (m, 4H).

Resolution of aminoalcohol 3

A mixture of **3** (60.7 g, 0.339 mol), (-)chlocyphos (93.5 g, 0.338 mol), and 675 mL 96% ethanol is brought to reflux. The solution is allowed to cool to rt with stirring. After stirring for 5 h the suspension is filtered, the solid being washed with 80 mL 1/1 water-ethanol. The yield is 38.53 g, 85 mmol, 25% with $[\alpha]_{578}$ -17.4° (c=0.5, methanol). This salt is stirred for 2 h with 400 mL 1 N sodium hydroxide solution and 200 mL dichloromethane. Water is added, the layers are separated and the aqueous layer is extracted with 3 x 150 mL dichloromethane. Washing with water, drying, evaporation and bulb-to-bulb distillation affords **3** as a solidifying oil (14.57 g, 81.4 mmol) with $[\alpha]_{578}$ 6.5° (c=0.5, methanol). The product is enantiomerically pure based on ^{1}H-NMR with $Eu(hfc)_3$ as a shift reagent. From the filtrate of the crystallization there could be obtained the optically enriched enantiomer which after treatment with 60 g (+)chlocyphos in 550 mL 96% ethanol gives 41.5 g (91 mmol, 27%)

salt with $[\alpha]_{578}$ 18.9°. This salt, on treatment with base, further workup and bulb-to-bulb distillation gives **3** as a solidifying oil (16.16 g, 90.3 mmol) with $[\alpha]_{578}$ -5.5°. The rotation of **3** is influenced by the presence of impurities (different runs gave varying rotations). Anal. Calcd. for $C_{11}H_{17}NO$ (mp 69-70°C): C, 73.70; H, 9.56; N, 7.81. Found: C, 73.52; H, 9.40; N, 7.73.

Resolution of aminoalcohol 4

A mixture of **4** (104.4 g, 0.489 mol), (+)phencyphos (115.0 g, 0.475 mol) and 550 mL 96% ethanol is brought to reflux. The solution is allowed to cool to rt with stirring, the solid is filtered off and washed with 100 mL 1/1 ethanol-ether and 100 mL ether. This gives 43.05 g (94.5 mmol, 19%) with $[\alpha]_{578}$ 20.4° (c=0.5, methanol). The filtrate of the crystallization is partially evaporated (about 400 mL solvent removed), then cooled to rt with stirring and addition of seed crystals. This affords another 30.17 g (66.2 mmol, 13%) of the salt with $[\alpha]_{578}$ 20.6°. The portions of the salt are combined and treated as described above for **3**. After bulb-to-bulb distillation **4** is obtained as a solidifying oil (33.42 g, 156.5 mmol) with $[\alpha]_{578}$ -29.1° (c=0.5, methanol). The product is enantiomerically pure based on ^{1}H-NMR with $Eu(hfc)_3$ as a shift reagent. From the filtrate of the crystallization there could be obtained the optically enriched enantiomer, which after treatment with (-)phencyphos by a similar procedure as above is transformed into (+)**4** with $[\alpha]_{578}$ 28.1°. Anal. Calcd. for $C_{11}H_{16}ClNO$ (mp 71-72°C): C, 61.82; H, 7.55; Cl, 16.59; N, 6.55. Found: C, 62.15; H, 7.62; Cl, 16.72; N, 6.47.

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