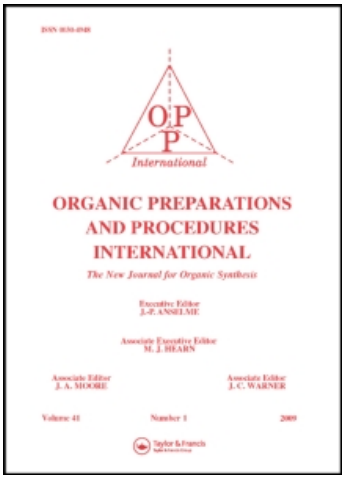


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

SYNTHESIS OF α-AMINOKETONES BY CATALYTIC HYDROGENATION OF BENZILMONOIMINES

Benito Alcaide[a]; Gerardo Escobar[a]; Rafael Pérez-Ossorio[a]; Joaquin Plumet[a]
[a] Departamento de Química Orgánica, Facultad de Química, Universidad Complutense, Madrid-3, SPAIN

To cite this Article Alcaide, Benito , Escobar, Gerardo , Pérez-Ossorio, Rafael and Plumet, Joaquin(1982) 'SYNTHESIS OF α-AMINOKETONES BY CATALYTIC HYDROGENATION OF BENZILMONOIMINES', Organic Preparations and Procedures International, 14: 3, 220 — 224
To link to this Article: DOI: 10.1080/00304948209354914
URL: http://dx.doi.org/10.1080/00304948209354914

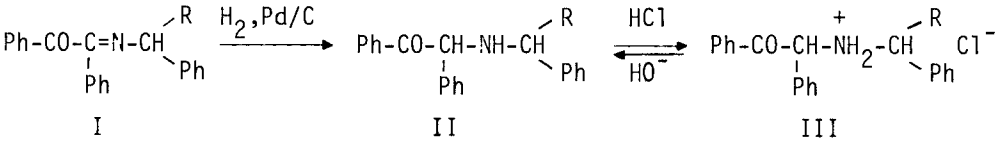
SYNTHESIS OF α-AMINOKETONES BY CATALYTIC HYDROGENATION OF BENZILMONOIMINES

Submitted by (10/2/81) Benito Alcaide, Gerardo Escobar, Rafael Pérez-Ossorio* and Joaquin Plumet.

Departamento de Química Orgánica, Facultad de Química, Universidad Complutense, Madrid-3, SPAIN.

α-Aminoketones are valuable intermediates in the synthesis of substances with adrenergic activity[1] and of various types of heterocycles.[2] For the synthesis of α-aminoketones various methods have been reported: alkylation of amines with α-haloketones,[3] reductive amination of α-diketones,[4] hydrolysis of α-(N-alkyl)-N-p-toluenesulphonylamino)ketones[5] and very recently reaction between α-bromoketones and imidates[6] and chromic oxidation of amino alcohols.[7]

As an alternative to these methods, we now report[8] a very simple synthesis which starts with a highly versatile reagent, the benzilmonoimines, easily obtainable by direct condensation of benzils with primary amines,[9] which upon catalytic hydrogenation yield the aminoketones. These aminoketones are unstable and revert slowly to the starting monoimines



I II III

a) R = H b) R = Me c) R = Et d) R = Pr^i e) R = Bu^t f) R = Ph
g) R = CH_2Ph IIh) PhCOCHPhNHPh IIi) p-TolylCOCH(p-Tolyl)NHMePh

TABLE I. Spectroscopic Properties for α-Aminoketones (II)

Cmpd	IR[a] ν(C=O)	IR[a] ν(NH)	^{1}H-NMR[b] δ ($CDCl_3$)
IIa	1680	3350	3.28 (s, 1H, NH); 3.65 (s, 2H, $PhCH_2$); 5.17 (s, 1H, NHCHCO); 6.9-7.8 (m, 15H, Ph).
IIb	1680	3340	1.3 and 1.4 (d, 3H, CH_3CH); 3.06 (s, 1H, NH); 3.40 and 3.68 (q, 1H, $CHCH_3$); 5.02 (s, 1H, NHCHCO); 6.7-7.4 (m, 15H, Ph).
IIc	1680	3330	0.7 and 0.8 (t, 3H, CH_3CH_2); 1.0-2.0 (m, 2H, CH_2CH_3); 3.30 (s, 1H, NH); 3.1-3.6 (m, 1H, $PhCHCH_2CH_3$); 5.13 (s, 1H, NHCHCO); 7.1-7.8 (m, 15H, Ph).
IId	1680	3340	0.6-1.2 (m, 6H, $(CH_3)_2CH$); 1.6-1.9 (m, 1H, $(CH_3)_2CH$); 3.03 and 3.33 (d, 1H, $PhCHPr^i$); 3.38 (s, 1H, NH); 5.00 (s, 1H, NHCHCO); 6.3-7.6 (m, 15H, Ph).
IIe	1675	3330	0.95 (s, 9H, $(CH_3)_3C$); 3.26 and 3.33 (s, 2H, overl, $PhCHBu^t$ and NH); 4.83 (s, 1H, NHCHCO); 6.6-7.5 (m, 15H, Ph).
IIf	1680	3340	3.40 (s, 1H, NH); 4.66 (s, 1H, $CHPh_2$); 5.17 (s, 1H, NHCHCO); 6.8-7.5 (m, 20H, Ph).
IIg	1675	3340	2.87 (app. t, 2H, CH_2Ph); 3.5-4.1 (m, 2H, NH and $PhCH_2CHPh$); 4.97 (s, 1H, NHCHCO); 6.7-7.5 (m, 20H, Ph)
IIh	1675	3330	4.5-4.8 (broad, 2H, NH and NHCHCO); 6.8-7.9(m, 15H,Ph)
IIi	1680	3350	1.27 and 1.33 (d, 3H, CH_3CH); 2.15 (s, 6H, CH_3Ar); 2.9-3.1 (broad, 1H, NH); 3.5 and 3.7 (q, 1H, $CHCH_3$); 4.95 (s, 1H, NHCHCO); 6.7-7.6 (m, 13H, aromatics).

a) Between KBr crystals. b) Duplication of some signals is due to the presence of stereoisomers.

on standing. However, bubbling hydrogen chloride through a freshly prepared ether solution of the aminoketone affords the related hydrochlorides as stable solids in excellent yields. High purity aminoketones can be recovered from the hydrochlorides by treatment with alkali. The general reaction as well as the various compounds prepared are shown above.

Spectral data of compounds II are collected in Table I and physical constants of compounds III are summarized in Table II.

TABLE II. α-Aminoketones Hydrochlorides (III)[a]

Cmpd	mp (C°)	Crystal. solvent	Formula	Elemental Analysis Calcd. (Found) C	H	Cl	N
IIIa	238-240	MeOH-Et_2O	$C_{21}H_{20}ClNO$	74.66 (74.42)	5.97 (5.82)	10.49 (10.64)	4.15 (4.11)
IIIb	222-224	MeOH-Et_2O	$C_{22}H_{22}ClNO$	75.09 (74.82)	6.30 (6.36)	10.08 (10.34)	3.98 (4.22)
IIIc	228-232	MeOH-Et_2O	$C_{23}H_{24}ClNO$	75.50 (75.46)	6.61 (6.70)	9.70 (10.06)	3.83 (3.56)
IIId	186-188	Ph-H	$C_{24}H_{26}ClNO$	75.87 (75.61)	6.90 (6.76)	9.33 (9.06)	3.69 (3.70)
IIIe	114-116	MeOH-Et_2O	$C_{25}H_{28}ClNO$	76.22 (76.08)	7.16 (7.20)	9.00 (9.29)	3.56 (3.69)
IIIg	202-204	Ph-H	$C_{28}H_{26}ClNO$	73.58 (73.69)	6.12 (6.06)	8.28 (8.47)	3.27 (3.31)
IIIh	180-182	crude	$C_{20}H_{18}ClNO$	74.18 (74.61)	5.60 (5.69)	10.95 (11.01)	4.32 (4.48)
IIIi	232-235	crude	$C_{23}H_{25}ClNO$	75.87 (75.36)	6.90 (7.02)	9.33 (9.26)	3.69 (3.74)

a) Attempts to isolate hydrochloride IIIf failed; spectra and analysis of the isolated product correspond to benzhydrilamine hydrochloride.
Calc. for $C_{13}H_{14}ClNO$: C, 71.03; H, 6.42; Cl, 16.15; N, 6.37.
Found : C, 70.76; H, 6.54; Cl, 15.88; N, 6.50.

EXPERIMENTAL

Monoimines (I).- Monoimines were prepared by refluxing equimolar amounts of benzil and the appropiate amine in benzene, toluene or xylene solution with removal of the water formed. Imine Ib has been described,[9a] Ic-f were reported in ref. 9b and Ii in ref. 9c. Yields of monoimines refer to crystalline product with correct microanalysis.

N-Benzyl-1-benzoylbenzylimine (Ia).- From benzil (12.25 g; 60 mmol) and benzylamine (6.42 g; 60 mmol) in toluene (100 ml); 4 hrs. Crystallized from methanol, mp. 78-79°; yield 9.17 g, 51%. IR: 1660, 1620 cm^{-1}. ^{1}H-NMR: δ 4.56 (s, 2H, $PhCH_2$); 7.0-7.8 (m, 15 H, Ph).

Anal. Calcd. for $C_{21}H_{17}NO$: C, 84.25; H, 5.72; N, 4.68.
Found: C, 84.21; H, 5.69; N, 4.71.

N-(1,2-Diphenyl)ethyl-1-benzoylbenzylimine (Ig).- From benzil (5.34 g; 25 mmol) and 1,2-diphenylethylamine (5.0 g; 25 mmol) in xylene (40 ml); 15 hrs. Crystallized from methanol, mp. 102-103°; yield 5.91 g, 61%. IR: 1665, 1630 cm^{-1}. ^{1}H-NMR: δ 3.1 (ABX system, part AB not resolved, 2H, $PhC\underline{H}_2$); (ABX system, part X not resolved, 1H, $PhC\underline{H}CH_2$); 6.6-7.8 (m, 20H, Ph).

Anal. Calcd. for $C_{28}H_{23}NO$: C, 86.35; H, 5.95; N, 3.60
Found: C, 86.41; H, 6.01; N, 3.56

N-Phenyl-1-benzoylbenzylimine (Ih).-From benzyl (15.0 g; 72 mmol) and aniline (6.67 g; 72 mmol) in xylene (30 ml); 7 hrs. Crystallized from ethanol, mp. 104-105°; yield 5.91 g, 42%. IR: 1665, 1620 cm^{-1}. ^{1}H-NMR: δ 6.9-7.7 (m, Ph).

Anal. Calcd. for $C_{20}H_{15}NO$: C, 34.19; H, 5.30; N, 4.91.
Found: C, 84.50; H, 5.53; N, 4.89.

Aminoketones (II).-Aminoketones were prepared by hydrogenation of monoimines (1 mmol) dissolved in ethyl acetate (50 ml) in the presence of 5% Pd/C (30-50 mg) at room temperature and an initial pressure of 40 psi (2.8 atm) in a Parr-type hydrogenator. When no more hydrogen was absorbed (2-16 hrs) the catalyst was filtered off and the solvent eliminated. The crude product was nearly pure aminoketone, yield 96-99%. In the IR spectrum no imine band was observed. ^{1}H-NMR spectrum showed only signals expected for aminoketones and the integrals are in agreement with the number of protons expected for each signal.

Attempt crystallization of the aminoketones failed and purification by chromatography could not be carried out due to the tendency to revert to the starting monoimine. However, the spectroscopic purity of the compounds

was highly satisfactory without purification.

The hydrochlorides III were prepared by bubbling hydrogen chloride through a solution of the aminoketone in ether and were crystallized from the solvents mentioned in Table II.

Acknowledgment.- G.E. expresses his gratitude for a scholarship from I.N.A.P.E. (Instituto Nacional de Asistencia y Promoción del Estudiante.

REFERENCES

1. See, for example: R.H. Uloth, J.R. Kirk, W.A. Gould and A.A. Larson, J. Med. Chem., 9, 88 (1966); A.A. Larson, W.A. Gould, H.R. Roth, W.T. Comer, R.H. Uloth, K.W. Dungan and P.M. Lish, ibid, 10, 462 (1967).

2. Reviews: A. Gossauer in "Die Chemie der Pyrrole", Springer Verlag, New York, 1974, p. 210; R.A. Jones and G.P. Bean in "The Chemistry of Pyrroles", Academic Press, London, 1977, p. 51.

3. See ref. 1 and G.K. Almstrom, Ann., 409, 291 (1915).

4. A. Skita, F. Keil and E. Baesler, Ber., 66, 858 (1933).

5. S. Gabriel, ibid, 47, 1336 (1914).

6. A. Guzman, J.M. Muchowski and N.T. Naal, J. Org. Chem., 46, 1224, (1981)

7. R.E. Lyle, J.R. Maloney and R.J. White, Org. Prep. Proced. Int., 12, 255 (1980).

8. A brief communication of this method was reported [B. Alcaide, R. Fernández de la Pradilla, C. López-Mardomingo, R. Pérez-Ossorio and J. Plumet, J. Org. Chem., 46, 3234 (1981)].

9. a) J.L. Garcia-Ruano and R. Pérez-Ossorio, An. Quim., 70, 617 (1974); b) R. Haro, R. Pérez-Ossorio, J. Plumet, J.L. García-Ruano and C. Pascual, ibid, 75, 165 (1979); c) J.L. García-Ruano, M.A. Henao, D. Molina, R. Pérez-Ossorio and J. Plumet, ibid, 76 C, 260 (1980).