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Easy one-pot conversion of 2-chlorohydrazone into 2-oxohydrazone derivatives via 2-azidohydrazone intermediates

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Abstract - The simple, mild and selective conversion in good yields of 2-chlorohydrazone into 2-oxohydrazone derivatives is reported. The reaction easily occurs via 2-azidohydrazone intermediates and represents a convenient procedure for the useful transformation of the methylene into carbonyl group.

INTRODUCTION

Hydrazone derivatives were demonstrated to be precious tools for the isolation, purification, and characterization of the carbonyl compounds. Indeed, these materials also show to be interesting products and powerful intermediates both for the protection as well as for the further modification of the carbonyl group.[1-4]

By continuing our previous investigations on the role of the hydrazine derivatives in organic chemistry,[3-5] we here report the selective conversion of the methylene group in α-position to the hydrazonic function into keto-group by treatment of the relevant

2-chlorohydrazone with sodium azide to give the related 2-azidohydrazone intermediate. Hydrolysis in situ of this intermediate directly affords under mild reaction conditions the carbonyl derivative in good yields. This procedure reveals to be compatible with other functional groups present in the substrate molecule.

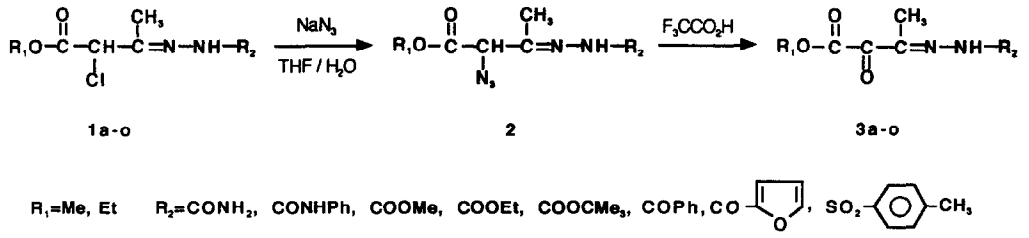
RESULTS AND DISCUSSION

1-Methyl-2-chloro-2-alkoxycarbonylhydrazones (**1a-o**) rapidly react (10-60 min) with sodium azide in tetrahydrofuran-water mixture to afford the respective 1-methyl-2-azido-2-alkoxycarbonylhydrazone (**2**) intermediates. The hydrolytic cleavage of the azido group of these intermediates is carried out in situ by addition of trifluoroacetic acid in order to obtain in one-flask the related 1-methyl-2-oxo-2-alkoxycarbonylhydrazones (**3a-o**), as pictured in Scheme. The presence of 2-azidohydrazones (**2**) in the reaction mixture is revealed by comparison with some authentic specimens (**2a-d**) prepared as reported in the notes.[6,7] These intermediates are stable and readily isolable products, while the others are not sufficiently stable materials.

Reaction conditions for the conversion of the 2-chlorohydrazones **1** into 2-azidohydrazones **2**, and of these latter compounds into 2-oxohydrazones **3** are pictured in Table. Yields, and melting points of the 2-oxohydrazones **3** are also listed in Table.

The reactions occur at room temperature with exception for the conversion of 2-chlorohydrazones **1k-n** into related 2-azidohydrazones (**2**) that require ice-cooling (about 5 °C). In most cases both reactions were complete within few hours (1-5 h) and do not require complicated procedures for the separation and isolation of the intermediates and/or the final products. The yields of the pure isolated products are in general high ranging between 73 and 94%, except for **3a** (66%), **3b** (62%), and **3o** (59%).

It is noteworthy that 2-oxohydrazones are not easily obtained by other methods, and especially by direct treatment of 1,2-diketones with hydrazine derivatives.[1,2] Furthermore, the 2-oxo-2-alkoxycarbonylhydrazones **3a-o** reported in this paper contain a system of three conjugated double bonds: the two different C=O (esteric and ketonic) and the C=N double bonds. It is well known that such a system may be useful in synthons for organic chemistry (i.e. for Michael-type, conjugate additions, (4+2) cycloadditions etc.).[1,2,9] Indeed, the products **3a-o** synthesized may be subjected to one of the numerous procedures described in the literature for the regeneration of the parent



Scheme

Table - Reaction conditions for the conversion of the 2-chlorohydrazones **1** into 2-azidohydrazones **2**, and of the 2-azidohydrazones **2** into 2-oxohydrazones **3**. Yields, and melting points of the 2-oxohydrazones **3**.

Entry	R_1	R_2	Reaction time (h)		Temperature (°C)		Yield[a] (%)	Mp[b] (°C)
			(1→2)	(2→3)	(1→2)	(2→3)	(3)	(3)
a	Me	$CONH_2$	1.0	16.0	r.t.	r.t.	66	179-180
b	Et	$CONH_2$	1.0	11.0	r.t.	r.t.	62	161-162
c	Me	CONHPh	0.8	20.0	r.t.	r.t.	90	184-185
d	Et	CONHPh	0.8	20.0	r.t.	r.t.	87	180-182
e	Me	COOMe	0.5	3.0	r.t.	r.t.	74	121-123
f	Me	$COOCMe_3$	1.0	4.0	r.t.	r.t.	73	105-106
g	Et	$COOCMe_3$	0.5	2.0	r.t.	r.t.	90	89-90
h	Et	COOEt	0.5	2.0	r.t.	r.t.	94	67-68
i	Et	COOMe	0.5	1.5	r.t.	r.t.	90	107-108
j	Me	COOEt	0.5	2.0	r.t.	r.t.	92	109-110
k	Me	COPh	0.2	0.5	5	r.t.	81	118-120
l	Et	COPh	0.2	1.5	5	r.t.	87	92-94
m	Et	CO-furyl	0.4	0.7	5	r.t.	90	147-148
n	Me	CO-furyl	0.4	1.0	5	r.t.	90	160-162
o	Me	SO_2-tolyl	0.5	18.0	r.t.	r.t.	59	150-151

[a]Yield of pure isolated product. [b]Melting points are uncorrected and often occur with decomposition.

carbonyl compounds giving interesting 1,2-dioxo-2-alkoxycarbonyl derivatives. No reaction worth mentioning by other functional group present in the starting molecules was revealed.

EXPERIMENTAL

2-Chlorohydrazones **1a–o** were prepared by reaction between α-chloroketones and hydrazines in accordance with methodologies previously reported.[3,5] α-Chloroketones, hydrazines, sodium azide, and trifluoroacetic acid were commercial materials (Aldrich or Janssen) and were used without further purification. Mps were determined in capillary tubes with a Büchi (Tottoli) apparatus, and are uncorrected. The products often decompose at melting point. IR spectra were obtained in Nujol mull with a Perkin-Elmer 298 spectrophotometer. ^{1}H NMR spectra at 60 MHz were recorded on a Varian EM-360L spectrometer, and at 200 MHz were recorded on a Bruker AC-200 in $CDCl_3$ or DMSO-d_6. Chemical shifts (δ) are reported in ppm downfield from internal TMS. The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; D_2O ex, D_2O exchange. Mass spectra were recorded on a Hewlett-Packard HP-5995. Merck precoated silica gel $60F_{254}$ plates (0.25 mm) were employed for analytical thin-layer chromatography (TLC), Merck silica gel PF_{254} plates (2.0 mm) for preparative TLC, and silica gel Kieselgel 60 (0.063–0.200 mm) for column chromatography. All the compounds prepared showed a satisfactory elemental analysis (C±0.35, H±0.30, N±0.30).

General procedure for the synthesis of 2-oxohydrazones 3a–o. To a stirred solution 2-chlorohydrazone (**1a–o**) (2 mmol), dissolved in tetrahydrofuran (5 ml), was added dropwise a solution of sodium azide (2.2 mmol) dissolved in water (0.5 ml) at room temperature or 5 °C (see Table). The reaction mixture was stirred (0.2–1.0 h) at the same temperature until the 2-chlorohydrazone converted into 2-azidohydrazone (**2**) (monitored by silica gel TLC). Trifluoroacetic acid (0.7 ml) was then added dropwise and the reaction was continued (0.5–20 h) under magnetic stirring until 2-azidohydrazone (**2**) completely converted into 2-oxohydrazone (**3a–o**) (monitored by silica gel TLC). At the end of the reaction, water (5 ml) was added, and the resulting mixture was concentrated under reduced pressure to about one half in volume. In the case of the 2-oxohydrazones **3e–o**, the mixture was extracted (3x30 ml) with appropriate solvent (methylene chloride for **2e–n**, ethyl acetate for **2o**). The organic phase was collected, dried with anhydrous sodium sulfate, and evaporated under reduced pressure, affording the crude products **3**. In the case of the 2-oxohydrazones **3a–d**, a white solid was formed during the above-mentioned volume concentration. This solid was filtered off by suction under reduced pressure. All the crude products **3** were purified by chromatography on a silica gel column (elution with ethyl ether-petroleum ether 40–60 °C mixtures for **3e–n**, with ethyl acetate-cyclohexane mixtures for **2a–d** and **2o**). The products **3** may be further purified by recrystallization from ethyl ether-petroleum ether 40–60 °C or tetrahydrofuran-cyclohexane.

3a: IR 3450, 3300, 3250, 3180, 1755, 1736, 1694, 1596, 1330, 1250, 1172, 1055 cm^{-1}; ^{1}H NMR (DMSO-d_6) 1.96 (3H, s), 3.85 (3H, s), 6.63 (2H, br s, D_2O ex), 10. 62 (1H, br s, D_2O ex) ppm; EI/MS: m/e 188 (M^++1), 128 (M-COOMe), 100 (M-CO-COOMe).

3b: IR 3460, 3300, 3250, 3180, 1746, 1730, 1695, 1596, 1324, 1245, 1170, 1050 cm^{-1}; ^1H NMR (DMSO-d_6) 1.27 (3H, t, J=7.0 Hz), 2.00 (3H, s), 4.33 (2H, q, J=7.0 Hz), 6.53 (2H, br s, D_2O ex), 10.77 (1H, br s, D_2O ex) ppm; EI/MS: m/e 202 (M^++1), 128 (M-COOEt), 100 (M-CO-COOMe).

3c: IR 3392, 3364, 3200, 3100, 1740, 1705, 1680, 1592, 1530, 1155, 1045 cm^{-1}; ^1H NMR (DMSO-d_6) 2.34 (3H, s), 3.95 (3H, s), 7.03-7.70 (5H, m), 8.77 (1H, br s, D_2O ex), 11.00 (1H, br s, D_2O ex) ppm; EI/MS: m/e 263 (M^+), 204 (M-COOMe), 176 (M-CO-COOMe).

3d: IR 3385, 3370, 3200, 3090, 1746, 1710, 1675, 1595, 1540, 1160, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) 1.37 (3H, t, J=7.0 Hz), 2.07 (3H, s), 4.42 (2H, q, J=7.0 Hz), 7.10-7.70 (5H, m), 8.80 (1H, br s, D_2O ex), 11.03 (1H, br s, D_2O ex) ppm; EI/MS: m/e 277 (M^+), 204 (M-COOEt), 176 (M-CO-COOEt).

3e: IR 3305, 1766, 1728, 1694, 1595, 1525, 1350, 1260, 1230, 1194, 1036 cm^{-1}; ^1H NMR ($CDCl_3$) 2.05 (3H, s), 3.87 (3H, s), 3.93 (3H, s), 9.10 (1H, br s, D_2O ex) ppm; EI/MS: m/e 203 (M^++1), 143 (M-COOMe), 115 (M-CO-COOMe).

3f: IR 3300, 1750, 1735, 1704, 1600, 1507, 1338, 1230, 1134, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) 1.57 (9H, s), 2.03 (3H, s), 3.92 (3H, s), 8.90 (1H, br s, D_2O ex) ppm; EI/MS: m/e 229 (M^+-Me), 185 (M-COOMe), 157 (M-CO-COOMe).

3g: IR 3291, 1736, 1724, 1690, 1595, 1512, 1338, 1270, 1232, 1140, 1038 cm^{-1}; ^1H NMR ($CDCl_3$) 1.43 (3H, t, J=7.0 Hz), 1.60 (9H, s), 2.08 (3H, s), 4.45 (2H, q, J=7.0 Hz), 9.12 (1H, br s, D_2O ex) ppm; EI/MS: m/e 260 (M^++2), 243 (M-Me), 185 (M-COOEt), 157 (M-CO-COOEt).

3h: IR 3290, 1750, 1735, 1692, 1596, 1521, 1336, 1252, 1225, 1185, 1038 cm^{-1}; ^1H NMR ($CDCl_3$) 1.33 (3H, t, J=7.0 Hz), 1.40 (3H, t, J=7.0 Hz), 2.05 (3H, s), 4.30 (2H, q, J=7.0 Hz), 4.41 (2H, q, J=7.0 Hz), 9.27 (1H, br s, D_2O ex) ppm; EI/MS: m/e 231 (M^++1), 157 (M-COOEt), 129 (M-CO-COOEt).

3i: IR 3296, 1760, 1736, 1690, 1597, 1525, 1336, 1260, 1230, 1200, 1038 cm^{-1}; ^1H NMR ($CDCl_3$) 1.40 (3H, t, J=7.0 Hz), 2.03 (3H, s), 3.87 (3H, s), 4.40 (2H, q, J=7.0 Hz), 9.23 (1H, br s, D_2O ex) ppm; EI/MS: m/e 217 (M^++1), 143 (M-COOEt), 115 (M-CO-COOMe).

3j: IR 3300, 1765, 1730, 1695, 1595, 1525, 1350, 1260, 1223, 1190, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) 1.33 (3H, t, J=7.0 Hz), 2.05 (3H, s), 3.91 (3H, s), 4.32 (2H, q, J=7.0 Hz), 9.22 (1H, br s, D_2O ex) ppm; EI/MS: m/e 217 (M^++1), 157 (M-COOMe), 129 (M-CO-COOMe).

3k: IR 3180, 1743, 1703, 1667, 1600, 1578, 1316, 1232, 1180, 1043 cm^{-1}; ^1H NMR ($CDCl_3$) 2.20 (3H, s), 3.63 (3H, s), 7.50 (3H, m), 7.83 (2H, m), 10.72 (1H, br s, D_2O ex) ppm; EI/MS: m/e 248 (M^+), 189 (M-COOMe), 161 (M-CO-COOMe).

3l: IR 3200, 1746, 1690, 1670, 1600, 1580, 1310, 1230, 1170, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) 1.12 (3H, t, J=7.0 Hz), 2.20 (3H, s), 4.12 (2H, q, J=7.0 Hz), 7.50 (3H, m), 7.83 (2H, m), 10.57 (1H, br s, D_2O ex) ppm; EI/MS: m/e 263 (M^++1), 189 (M-COOEt), 161 (M-CO-COOEt).

3m: IR 3180, 1739, 1706, 1682, 1606, 1560, 1307, 1236, 1180, 1120, 1056 cm^{-1}; ^1H NMR ($CDCl_3$) 1.37 (3H, t, J=7.0 Hz), 2.20 (3H, s), 4.40 (2H, q, J=7.0 Hz), 6.60 (1H, q, J=4.0 and 2.0 Hz), 7.46 (1H, d, J=4.0 Hz), 7.67 (1H, d, J=2.0 Hz), 9.87 (1H, br s, D_2O ex)

ppm; EI/MS: m/e 253 (M^++1), 179 (M-COOEt), 151 (M-CO-COOEt).

3n: IR 3180, 1746, 1708, 1662, 1613, 1562, 1316, 1240, 1180, 1162, 1120, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) 2.20 (3H, s), 3.93 (3H, s), 6.63 (1H, q, J=4.0 and 2.0 Hz), 7.45 (1H, d, J=4.0 Hz), 7.70 (1H, d, J=2.0 Hz), 9.83 (1H, br s, D_2O ex) ppm; EI/MS: m/e 238 (M^+) 179 ((M-COOMe), 151 (M-CO-COOMe).

3o: IR 3180, 1732, 1708, 1600, 1360, 1340, 1260, 1170, 1086, 1046 cm^{-1}; ^1H NMR (DMSO-d_6) 1.93 (3H, s), 2.40 (3H, s), 3.83 (3H, s), 7.35 (1H, br s, D_2O ex), 7.47 (2H, d, J=8.0 Hz), 7.80 (2H, d, J=8.0 Hz) ppm; EI/MS: m/e 299 (M^++1), 239 (M-COOMe), 211 (M-CO-COOMe).

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References and Notes

1. E. W. Schmidt, "Hydrazine and its derivatives. Preparation, properties, applications.", Interscience Publishers, John Wiley & Sons, New York, 1984; P. A. S. Smith, "Derivatives of hydrazine and other hydronitrogens having N-N bonds.", The Benjamin-Cummings Publishing Company, Reading, 1983; and the references cited therein.
2. S. Patai, ed., "The chemistry of the carbon-nitrogen double bond.", Interscience Publishers, John Wiley & Sons, New York, 1970; Ibid., "The chemistry of hydrazo, azo and azoxy groups.", ibid., New York, 1975; Ibid., "The chemistry of double-bonded functional groups.", ibid., New York, 1977 (Supplement A); and the references cited therein.
3. O. Attanasi, Chim. Ind. (Milan), **66**, 9 (1984); O. Attanasi and L. Caglioti, Org. Prep. Proced. Int., **18**, 299 (1986); and the references cited therein.
4. O. Attanasi, P. Filippone and S. Santeusanio, Tetrahedron Lett., 5787 (1988); O. Attanasi, P. Filippone, A. Mei, A. Bongini and E. Foresti, Tetrahedron, **46**, 5685 (1990); O. Attanasi, P. Filippone and A. Mei, J. Chem. Research (S), 252 (1991).
5. See inter alia: O. Attanasi and S. Gasperoni, Gazz. Chim. Ital., **108**, 137 (1978); O. Attanasi, S. Gasperoni and C. Carletti, Chim. Ind. (Milan), **60**, 654 (1978); O. Attanasi, S. Gasperoni and C. Carletti, J. Prakt. Chem., **322**, 1063 (1980); O. Attanasi, M. Grossi and F. Serra-Zanetti, J. Chem. Research (S), 322 (1983); and the references cited therein.
6. Conjugated azoalkenes **4a-d**, prepared by dehydrohalogenation of the related 2-chlorohydrazones **1a-d**,[7] smoothly provide the 2-azidohydrazones **2a-d** by treatment with hydrazoic acid, according to previous findings on arylazo-glycenosides.[8] In a typical experiment, to a stirred solution of conjugated azoalkene (**4**) (1 mmol) dissolved in acetonitrile (3 ml) (**4a-b**) or benzene (5 ml) (**4c-d**) was slowly added dropwise a solution of hydrazoic acid in benzene at room temperature until the conjugated azoalkene completely disappeared (monitored by silica gel TLC). At the end of the reaction (0.7 h) the solution becames colourless. The products **2a-d** in good purity were obtained in nearly quantitative yield (96-99%) by evaporation of the solvent under reduced pressure at room temperature. The products **2a-d** may be further purified by crystallization from methylene chloride-petroleum ether 40-60 °C. **2a**: Mp 96-98 °C; IR 3480, 3260, 3224, 3160, 2130, 1745, 1710, 1580, 1220 cm^{-1}; ^1H NMR (DMSO-d_6) 1.90 (3H, s), 3.80 (3H, s), 4.87 (1H, s), 6.30 (2H, br s, D_2O ex), 9.58

(1H, br s, D_2O ex) ppm. **2b**: Mp 91-93 °C; IR 3480, 3282, 3160, 2116, 1755, 1745, 1590, 1296, 1200 cm^{-1}; ^1H NMR ($CDCl_3$) 1.33 (3H, t, J=7.0 Hz), 2.00 (3H, s), 4.28 (2H, q, J=7.0 Hz), 4.42 (1H, s), 5.97 (2H, br s, D_2O ex), 9.67 (1H, br s, D_2O ex) ppm. **2c**: Mp 127-129 °C; IR 3400, 3205, 3100, 2108, 1740, 1695, 1594, 1540, 1215 cm^{-1}; ^1H NMR ($CDCl_3$) 2.17 (3H, s), 3.90 (3H, s), 4.52 (1H, s), 7.10-7.70 (5H, m), 8.23 (1H, br s, D_2O ex), 10.27 (1H, br s, D_2O ex) ppm. **2d**: Mp 115-117 °C; IR 3394, 3200, 3100, 2110, 1748, 1692, 1594, 1543, 1210 cm-1; ^1H NMR ($CDCl_3$) 1.33 (3H, t, J=7.0 Hz), 2.13 (3H, s), 4.32 (2H, q, J=7.0 Hz), 4.45 (1H, s), 7.03-7.67 (5H, m), 8.18 (1H, br s, D_2O ex), 10.07 (1H, br s, D_2O ex) ppm.

7. O. Attanasi, P. Filippone, A. Mei and S. Santeusanio, Synthesis, 671 (1984).
8. P. M. Collins, D. Gardiner, S. Kumar and W. G. Overend, J. Chem. Soc., Perkin Trans. 1, 2596 (1972); P. M. Collins, J. R. Hurford and W. G. Overend, ibid., 1975 (1975); P. M. Collins, W. G. Overend and V. M. Racz, Carbohydrate Research, **45**, 127 (1975); G. S. Hajivarnava, W. G. Overend and N. R. Williams, J. Chem. Soc., Perkin Trans. 1, 205 (1982).
9. F. Fringuelli and A. Taticchi, "Dienes in the Diels-Alder reaction.", Interscience Publishers, John Wiley & Sons, New York, 1990; and the references cited therein.