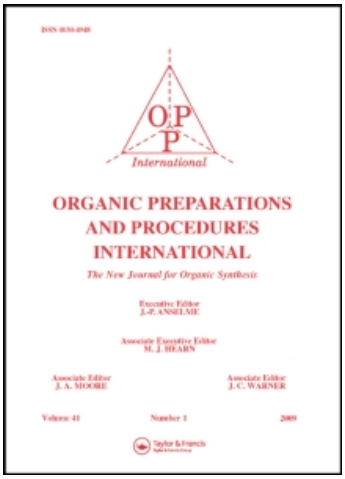


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

A CONVENIENT SYNTHESIS OF 3, 5-DIMETHYL-4-ISOXAZOLYL AND OF 3, 5-DIMETHYL-4-ISOTHIAZOLYLKETONES

Angel Alberola[ab]; Purificacion Cuadrado[ab]; Ma Carmen Sañudo[ab]; Tomás Torroba[ab]
[a] Departamento de Química, Orgánica Universidad de Valladolid, Valladolid, SPAIN [b] Departamento de Química, Facultad de Veterinaria, Universidad de Extremadura, Caceres, SPAIN

To cite this Article Alberola, Angel , Cuadrado, Purificacion , Sañudo, Ma Carmen and Torroba, Tomás(1988) 'A CONVENIENT SYNTHESIS OF 3, 5-DIMETHYL-4-ISOXAZOLYL AND OF 3, 5-DIMETHYL-4-ISOTHIAZOLYLKETONES', Organic Preparations and Procedures International, 20: 4, 377 — 383
To link to this Article: DOI: 10.1080/00304948809355880
URL: http://dx.doi.org/10.1080/00304948809355880

ORGANIC PREPARATIONS AND PROCEDURES INT. 20(4), 377-383 (1988)

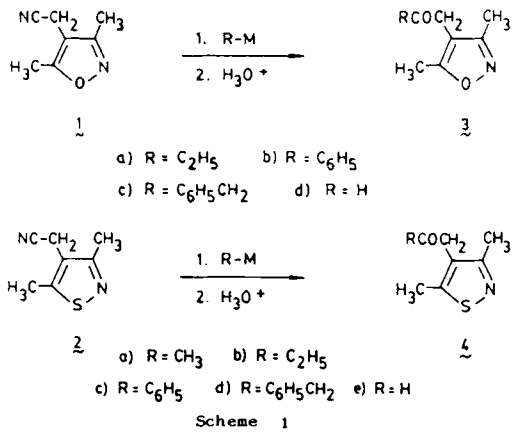
A CONVENIENT SYNTHESIS OF 3,5-DIMETHYL-4-ISOXAZOLYL AND OF 3,5-DIMETHYL-4-ISOTHIAZOLYLKETONES.

Angel Alberola*, Purificación Cuadrado,
Mª Carmen Sañudo and Tomás Torroba

Departamento de Química Orgánica
Universidad de Valladolid, 47011 Valladolid, SPAIN

Departamento de Química, Facultad de Veterinaria,
Universidad de Extremadura, Caceres, SPAIN

Isoxazolyl- and isothiazolylacetic acid derivatives and the corresponding α-aminoacids have been employed as precursors in the preparation of various cephalosporanic, penicillanic acids and natural products.[1] We have previously reported several synthetic routes to 4-acyl- and 4-alkylisoxazoles and isothiazoles.[2] It became of interest to devise new methods for the preparation of 3,5-dimethyl-4-isoxazolyl and 3,5-dimethyl-4-isothiazolylketones. This paper reports a new method for the preparation of 3,5-dimethyl-4-isoxazolyl and 3,5-dimethyl-4-isothiazolylacetonitrile (1 and 2 respectively) and the reaction of 1 and 2 with organoaluminium and organomagnesium com-



Scheme 1

pounds to give alkyl-(3,5-dimethyl-4-isoxazolylmethyl) and alkyl-(3,5-dimethylisothiazolylmethyl)-ketones in high yields.

Compound 1 was prepared from 3,5-dimethyl-4-chloromethylisoxazole by reaction with sodium cyanide and isothiazole 2, was obtained by dehydration of the corresponding 3,5-dimethyl-4-isothiazolylacetamide with phosphorous oxychloride. Treatment of 1 and 2 with Grignard reagents and organoaluminium compounds afforded the ketones listed in Table 1. Yields were higher when organoaluminium compounds were used instead of organomagnesium compounds. As expected, the reaction of 1 and 2 with tri-isobutylaluminium led to acetaldehyde derivatives (3d and 4e, respectively) via hydride transfer.

EXPERIMENTAL SECTION

Melting points were determined on a Buchi apparatus and are uncorrected as are the boiling points. IR spectra were recorded using a Pye-Unicam SP-1100 spectrometer and the ^{1}H-NMR spectra were performed on a Varian T-60 A instrument; chemical shifts are expressed in ppm relative to TMS as internal standard. Mass spectra were obtained on a Hewlett-Packard 5946-A instrument.

3,5-Dimethyl-4-isoxazolylacetonitrile (1).- Sodium cyanide (5.9g, 0.12 mole) in dimethyl sulfoxide (25 ml) was added dropwise to 14.5g (0.1 mole) of 4-chloromethyl-3,5-dimethylisoxazole.[4] The resulting suspension was stirred at 50-60º for 3 hrs, and then diluted with water and extracted with ether. The solvent was removed and the product was purified to yield 10.9g (80%) of colorless liquid, bp.110-112º/2mm; 82-83º/0.2mm.[5]

Anal. Calcd. for $C_7H_8N_2O$: C,61.76; H,5.88; N,20.59
Found: C,61.69; H,5.93; N,20.50%.

MS (75 eV), m/e(%): 136(M^+,21), 121(20), 43(100), 42(29). IR(film): 2270 cm^{-1}. ^{1}H-NMR(CCl_4): δ 2.20(s,3H), 2.35(s,3H), 3.30(s,2H).

3,5-Dimethyl-4-isothiazolylacetamide.- Ethyl 3,5-dimethyl-4-isothiazolylacetate[6] (6.0g, 0.03 mole) and saturated aqueous

TABLE 1. Reactions of 1 and 2 with Organometallic Compounds.

Substrate	R-M	Solvent	Time(hr)/ temp.(ºC)	Products(%)[a]
1	$EtMgBr^b$	Ether	9/36	3a(10), 1(75).
1	$EtMgBr^b$	Benzene	16/78	3a(15), 1(65).
1	$EtMgBr^b$	Toluene	30/110	3a(20), 1(45).
1	$EtMgBr^c$	Ether	30/36	3a(30), 1(45).
1	$PhMgBr^b$	Ether	9/36	3b(5), 1(75).
1	$PhMgBr^c$	Benzene	30/78	3b(25), 1(40).
1	$PhCH_2MgCl^c$	Benzene	30/78	3c(25), 1(40).
1	Et_3Al^c	Benzene	30/78	3a(80).
1	$^iBu_3Al^c$	Benzene	30/78	3d(80).
2	$MeMgI^c$	Ether	8/36	4a(23), 2(40).
2	$EtMgBr^c$	Ether	8/36	4b(18), 2(60).
2	$PhMgBr^c$	Ether	20/36	4c(12), 2(65).
2	$PhMgBr^c$	Benzene	30/78	4c(42), 2(10).
2	$PhCH_2MgCl$	Benzene	30/78	4d(51), 2(10).
2	Me_3Al^c	Benzene	20/78	4a(55), 2(5).
2	Et_3Al^c	Benzene	20/78	4b(76).
2	$^iBu_3Al^c$	Benzene	20/78	4e(63).

a) Yields refer to isolated pure compounds b) Molar ratio substrate:organometallic = 1:1 c) Molar ratio substrate:organometallic = 1:3.

ammonia solution (7,5 ml), previously cooled at 0ºC, were mixed and stoppered at this temperature for 18 hrs. The lower layer was then dissolved by stirring, and the resulting solution, saturated again with gaseous ammonia and kept closed at room temperature until the amide crystals began to appear. The precipitation was completed by external cooling at about 0º, and the solid collected, recrystallized from water and dried in a vacuum dissicator at 80º to yield 5.0g (98%) of white needles, mp. 146-147º.

Anal. Calcd. for $C_7H_{10}N_2OS$: C,49.38; H,5.92; N,16.45
Found: C,49.34; H,5.87; N,16.40%.

IR(KBr): 3380, 3150, 1690 cm^{-1}. ^{1}H-NMR(CD_3SOCD_3): δ 2.35(s,3H), 2.45(s,3H), 3.45(s,2H), 10.20(br s,2H).

TABLE 2. Alkyl-(3,5-dimethyl-4-isoxazolylmethyl) and Alkyl-(3,5-dimethyl-4-isothiazolylmethyl)ketones.

Compound	mp or bp/Torr (ºC)	IR [cm^{-1}] (film or KBr)	^{1}H-NMR [ppm] $CDCl_3$
3a	35-36[a]	1720(C=O)	1.00(t,3H),2.00(s,3H), 2.20(s,3H),2.35(q,2H), 3.30(br s,2H).
3b	125-126[a]	1620(C=O)	2.15(s,3H),2.30(s,3H), 3.95(s,2H),7.40(m,3H), 7.85(m,2H).
3c	58-59[a]	1740(C=O)	1.85(s,3H),2.00(s,3H), 3.20(s,2H),3.50(s,2H), 7.00(m,5H).
3d[b]	98-100/2	2850,2750(HC=O) 1720(C=O)	2.10(s,3H),2.30(s,3H), 3.40(d,2H),9.60(t,1H).
4a	86-87/0.5	1730(C=O)	2.10(s,3H),2.30(s,3H), 2.40(s,3H),3.55(s,2H).
4b[c]	80-81/0.5	1720(C=O)	1.20(t,3H),2.45(s,3H), 2.60(s,3H),2.60(q,2H), 3.75(s,2H).
4c[d]	129-130[e]	1690(C=O)	2.45(s,3H),2.50(s,3H), 4.35(s,2H),7.70(m,3H), 8.10(m,2H).
4d[f]	62-63[e]	1730(C=O)	2.15(s,3H),2.20(s,3H), 3.50(s,2H),3.65(s,2H), 7.20(m,5H).
4e[g]	80-81/0.4	2720(HC=O) 1730(C=O)	2.35(s,3H),2,45(s,3H), 3.60(d,2H),9.60(t,1H).

a)From ethanol b)2,4-DNPH, mp.180-181ºC(ethanol) c)2,4-DNPH, mp.124-125ºC(ethanol) d)2,4-DNPH, mp.208-209ºC(methanol) e)From benzene f)2,4-DNPH, mp.145-146ºC(ethanol) g)2,4-DNPH, mp.189-190ºC(ethanol).

3,5-Dimethyl-4-isothiazolylacetonitrile (2).- 3,5-Dimethyl-4-

isothiazolylacetamide (3.0g, 0.01 mole) was suspended in 8.7g (0.072 mole) of phosphorous oxychloride. The mixture was heated at 100º for 5 hrs, and then the oxychloride remainder distilled off. The residue was poured over 30g of ice-water, and the resulting aqueous solution extracted with 20 ml of ether. The solvent was removed, and the solid recrystallized from benzene:hexane. Nitrile 2 was obtained as colorless plates, mp.63--64º. Yield, 1.2g (93%).

Anal. Calcd. for $C_7H_8N_2S$: C,55.23; H,5.29; N,18.40
Found: C,55.30; H,5.21; N,18.39%.

IR(KBr): 2260, 1560 cm^{-1}. ^{1}H-NMR(CCl_4): δ 2.50(s,3H), 2.55(s,3 H), 3.55(s,2H).

Reactions with Grignard Reagents. General Procedure.- Grignard reagents were prepared as usual from 0.06 atom-g of magnesium and 0.056 mole of the corresponding organic halide, in 40 ml of dry ether. After cooling at 0º, 0.056 mole of the substrate (1 or 2) were dissolved in 40 ml of the appropriate solvent (Table 1), and added dropwise. The mixture was heated at reflux for 3 hrs with stirring, then hydrolyzed at 0º with diluted HCl. The organic layer was separated and the ketone liberated from the ketenimine hydrochloride by heating the aqueous layer at reflux for 1 hr. Compounds 3a, 3b, 3c, 4a, 4b, 4c and 4d were isolated in the usual way and porufied by recrystallization or distillation at reduced pressure. Physical and spectral data for these compounds are listed in Table 2. When the reactions were carried out in solvents other than ether, it was changed before adding the substrte 1 or 2.

Reactions with Organoaluminium Compounds. General Procedure.- The substrate (1 or 2)(0.014 mole) in 10 ml of solvent (Table 1) was added during 30 min. to a stirred solution of organoaluminium compound (0.04 mole) in 65 ml of the same solvent, and the mixture heated at reflux for 30 hrs. After cooling at

0º, it was hydrolyzed with diluted HCl, the organic layer separated and dried over magnesium sulfate. Compounds 3a, 3d, 4a, 4b and 4e were isolated in the usual way, and purified by distillation at reduced pressure. Their physical and spectral data are listed in Table 2.

TABLE 3. Elemental Analyses Data.

Product No.	Molecular Formula	Elemental Analysis
3a	$C_9H_{13}NO_2$	Calcd.: C,64.69;H,7.78;N,8.38 Found : C,64.61;H,7.71;N,8.29
3b	$C_{13}H_{13}NO_2$	Calcd.: C,72.57;H,6.04;N,6.51 Found : C,72.51;H,6.07;N,6.45
3c	$C_{14}H_{15}NO_2$	Calcd.: C,73.38;H,6.55;N,6.11 Found : C,73.25;H,6.62;N,5.99
3d	$C_7H_9NO_2$	Calcd.: C,60.43;H,6.47;N,10.07 Found : C,60.38;H,6.51;N,10.09
4a	$C_8H_{11}NOS$	Cacld.: C,56.80;H,6.50;N,8.28 Found : C,56.75;H,6.52;N,8.19
4b	$C_9H_{13}NOS$	Calcd.: C,59.01;H,7.10;N,7.65 Found : C,59.12;H,7.07;N,7.61
4c	$C_{13}H_{13}NOS$	Calcd.: C,67.50;H,5.66;N,6.05 Found : C,67.42;H,5.69;N,6.10
4d	$C_{14}H_{15}NOS$	Calcd.: C,68.53;H,6.16;N,5.70 Found : C,68.51;H,6.09;N,5.77
4e	C_7H_9NOS	Calcd.: C,54.19;H,5.80;N,9.03 Found : C,54.23;H,5.74;N,8.97

Acknowledgement.- The authors are indebted to Comisión Asesora de Investigación Científica y Técnica for financial support (Grant 3086/83).

REFERENCES

1. a) F. P. Doyle, A. A. W. Long, J. H. C. Nayler and E. R. Stove, Nature, 192,1183(1961); b) G. Cantarelle, M. Carissimi and F. Ravennena, Farmaco ed. Sci., 30 (2),128(1975); c) R. V. Lemieux and R. Raap, R and L Molecular Research Ltd. Japan Pat.,77.31.345(1977)(Chem. Abstr. 88:p 190810b); d) R.

Raap, J. Antibiot., 24,697(1971)(Chem. Abstr. 76:14409w); e) R. Raap and R. Rintje, R and L Molecular Research Ltd. U.S. Pat. 3.579.506(1968)); f) T. S. Gardner, E. Wenis and J. Lee J.Org.Chem., 26,1514(1961); g) L. O. Randall and R. E. Bagdon, Ann. N. Y. Acad. Sci., 80,626(1959); h) N. K. Kochetkov Österr. Chemiker-Ztg., 62,276(1961); i) W. M. Welch, Synthetic Commun., 12(14), 1089(1982); j) J. E. Baldwin, S. B. Haber and J. Kitchin, J.Chem.Soc.Chem.Commun., 790(1973); k) A. Yoshida, S. Oida and E. Ohki, Chem.Pharm.Bull., 24,362 (1976); 1) J. W. Scott and A. Boris, J.Medicinal Chem., 16, 512(1973); m) J. A. McFadzean and S. Squires, Nature, 204, 4958(1964).

3. a) A. Alberola, A. M. González, M. D. Guerra, F. J. Pulido and J. F. Rodriguez, Anales de Química, 80 C, 59(1984); b) A. Alberola, A. M. González and T. Torroba, Anales de Química, 80 C, 181(1984); c) A. Alberola, F. Alonso, J. M. Bañez, P. Cuadrado, F. A. Mocha and M. C. Sañudo, Anales de Química, C (1986)(in press); d) A. Alberola, F. Alonso, P. Cuadrado and M. C. Sañudo, Synthetic Commun., 17(10), 1207 (1987).
4. N. K. Kochetkov, E. D. Khomutova and M. V. Bazilevsky, Zhur. Obshchei Khim., 28, 2736(1958).
5. T. Torroba, Doctoral Thesis, Valladolid 1982.
6. P. Cuadrado, Doctoral Thesis, Valladolid 1985.

(Received July 27, 1987; in revised form November 17, 1987)