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SIMPLE SYNTHESIS OF α-METHYLENE ESTERS AND AMIDES FROM METHACRYLIC DERIVATIVES VIA TOSYLATED INTERMEDIATES

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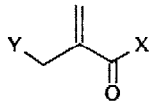
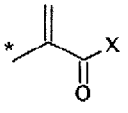
Summary: α-(Tosylmethyl)acrylic acid methyl ester or N-isopropylamide (obtained by a tandem iodosulfonylation-dehydroiodination of methyl methacrylate or N-isopropylacrylamide) react with Grignard reagents or sodium diethyl malonate to give the corresponding α-methylene esters or amides in a regioselective manner.

The importance of acrylates and related compounds in organic chemistry is due not only to the large number of naturally occurring compounds bearing this functionality[1] but also to their utility as synthetic intermediates, specially in Michael-type reactions. The synthesis of α-methylene carbonyl compounds has recently been carried out starting from α-substituted acrylic derivatives of the type **1**; thus, compounds **1** with Y = Bu_3Sn,[2] $PhSO_2$,[3] and PhS[4] have been used in the preparation of α-methylene γ-lactones,[2b-d] β-lactams,[3a] esters and amides,[2a,3c] and other different systems such as dihydropyrans,[3b] (E)-α,β-unsaturated amides,[3b] and cyclopentenes.[3d,4] In all cases compounds **1** act as the corresponding radical (**2a**)[2a] or anionic (**2b**)[2-4] synthons. On the other hand, acetoxy or bromo esters of the type **1** with Y = OAc,[5] Br[6] have been used recently as cationic equivalents **2c** for the synthesis of α-methylene esters by reaction with organometallic reagents. In these cases either alkylic magnesium[5] or benzylic zinc[6] compounds work only in the presence of catalytic[5] or stoichiometric[6] amount of a copper salt at temperatures below -70°C to avoid by-reactions. We report here a new synthesis of α-methylene esters and amides **3** using tosylated derivatives of the type **1** (Y = Ts) as cationic equivalents **2c** and Grignard reagents or sodium malonate.



1



2a, * = ·
2b, * = -
2c, * = +

The treatment of methyl 2-(tosylmethyl)acrylate (**1a**) or N-isopropyl-2-(tosylmethyl)-acrylamide (**1b**) with different Grignard reagents or sodium diethyl malonate in tetrahydrofuran at low temperature gave α-methylene esters or amides **3** in a regioselective manner (Scheme 1 and Table 1). In both cases (**1a** or **1b**), two equivalents of the corresponding organomagnesium

compound have to be used in order to obtain the best yields. When butyl or allylmagnesium bromide were used in the reaction with the ester derivative **1a**, the addition to the ester group was mainly observed leading to the corresponding alcohol. This problem could be circumvented in the case of the butyl derivative by adding copper(I) bromide[5] to the reaction mixture before the treatment with the Grignard reagent; so, the expected product **3d** was exclusively obtained.

Table 1. Reaction of tosylated derivatives **1** with organometallic reagents. Synthesis of α-methylene esters and amides **3**

Starting material	Organometallic RM	Reaction temperature (°C)	Product[a] No.	Yield (%)[b]	B.p. (°C)[c] or R_f[d]
1b	CH_2=CHMgBr	-30	**3a**	40	0.50
1b	EtMgBr	-30	**3b**	73	0.50
1b	CH_2=$CHCH_2$MgBr	-30	**3c**	87	0.53
1a	Bu^nMgBr[e]	-40[f]	**3d**	88	60
1a	PhMgCl	0	**3e**	68	120
1b	PhMgCl	-30	**3f**	61	0.66
1a	$(EtO_2C)CHNa$[g]	0	**3g**	91	150
1b	$(EtO_2C)CHNa$[g]	-15	**3h**	70	0.67

[a] All compounds were >95% pure (g.l.c. and/or n.m.r.) and gave satisfactory spectral data (i.r., ^{1}H n.m.r., and mass spectra).

[b] Based on the starting material **1**. Yields after distillation or flash chromatography (silica gel, hexane/ethyl acetate).

[c] Bath temperature at 0.1 torr.

[d] Silica gel, hexane/ethyl acetate: 1/1.

[e] Copper(I) bromide (1:0.5 molar ratio) was added.

[f] The temperature was allowed to rise to -20°C during 3 hours.

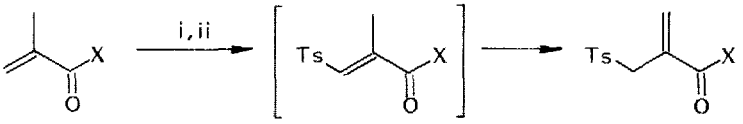
[g] Prepared from diethyl malonate and sodium hydride in tetrahydrofuran just before the reaction with compound **1**.

1a, X = OMe
1b, X = NHPr^{i}

3a-h

Scheme 1.

Starting materials **1a** and **1b** were prepared[7] by an one-pot procedure starting from the corresponding methacrylic acid derivatives **4** and using a tandem iodosulfonylation-dehydroiodination reaction[8a,9] (Scheme 2). This process afford first compounds **5**,[8] but they isomerize to the thermodynamically more stable[10] products **1** under the basic conditions during the second step of the process, when long reaction times (2-3 days) were used.



4a,b **5a,b** **1a,b**

Scheme 2. Reagents: i, NaTs-I_2; ii, Et_3N.

The simple methodology described in this paper allows the alkylation of methacrylic acid derivatives at the methyl group through a two steps procedure involving tosylated intermediates.

In a typical reaction to a solution of compound **1** (1 mmol) in tetrahydrofuran (5 ml) was added the corresponding Grignard reagent (2 mmol) or sodium diethyl malonate (1 mmol; see footnote g in Table 1) at low temperature (see Table 1) under argon. After 1 h stirring the reaction mixture was hydrolyzed with water and a saturated aqueous solution of ammonium chloride, and extracted with ether. The organic layer was dried over anhydrous sodium sulfate and evaporated (15 torr) to afford crude products **3**, which were purified by distillation in vacuo (0.1 torr) or by flash chromatography on silica gel (see footnote d in Table 1).[11,12]

References and Notes

1. (a) H. M. R. Hoffmann and J. Rabe, Angew. Chem. Int. Ed. Engl., **1985**, 24, 94; (b) N. Petragnani, H. M. C. Ferraz, and G. V. J. Silva, Synthesis, **1986**, 157.

2. (a) J. E. Baldwin, R. M. Adlington, D. J. Birch, J. A. Crawford, and J. B. Sweeney, J. Chem. Soc., Chem. Commun., **1986**, 1339; (b) J. E. Baldwin, R. M. Adlington, and J. B. Sweeney, Tetrahedron Lett., **1986**, 27, 5423; (c) K. Tanaka, H. Yoda, Y. Isobe, and A. Kaji, J. Org. Chem., **1986**, 51, 1856; (d) J. Nokami, T. Tamaoka, H. Ogawa, and S. Wakabayashi, Chem. Lett., **1986**, 541.

3. (a) K. Tanaka, H. Horiuchi, and H. Yoda, J. Org. Chem., **1989**, 54, 63; (b) K. Tanaka, H. Yoda, and A. Kaji, Tetrahedron Lett., **1985**, 26, 4747; (c) K. Tanaka, H. Yoda, and A. Kaji, Tetrahedron Lett., **1985**, 26, 4751; (d) P. Beak and D. A. Burg, Tetrahedron Lett., **1986**, 27, 5911.
4. P. Beak and K. D. Wilson, J. Org. Chem., **1987**, 52, 218.
5. H. Amri, M. Rambaud, and J. Villieras, J. Organometal. Chem., **1986**, 308, C27.
6. S. C. Berk, P. Knochel, and M. C. P. Yeh, J. Org. Chem., **1988**, 53, 5789.
7. N,N-Diisopropyl-2-(phenylsulfonylmethyl)acrylamide (**1**, X = NPr^i_2, Y = $PhSO_2$)[3d] and ethyl 2-(phenylsulfonylmethyl)acrylate (**1**, X = OEt, Y = $PhSO_2$)[2a] have been previously prepared starting from 2-(bromomethyl)acrylic acid or its ethyl ester, respectively. N-Phenyl-2-(phenylsulfonylmethyl)acrylamide (**1**, X = NHPh, Y = $PhSO_2$)[3b] has also been prepared from N-phenyl-2-(tributylstannylmethyl)acrylamide.
8. For preparation and synthetic applications of these compounds as β-acylvinyl cation equivalents see: (a) C. Nájera, B. Baldó, and M. Yus, J. Chem. Soc., Perkin Trans. 1, **1988**, 1029; (b) C. Nájera and M. Yus, Tetrahedron Lett., **1989**, 30, 173.
9. Compound **1a**: 65% yield, m.p. 41°C (hexane-dichloromethane). Compound **1b**: 51% yield, m.p. 122-123°C (hexane-dichloromethane).
10. P. D. Magnus, Tetrahedron, **1977**, 33, 2019.
11. ^{1}H n.m.r. data for compounds **1** and **3** (60 MHz, CCl_4-TMS):
1a: 2.4 (s, 3H, CH_3Ar), 3.35 (s, 3H, CH_3O), 4.0 (s, 2H, CH_2S), 5.75, 6.3 (2 s, 2H, CH_2=C), 7.2, 7.6 (2 d, J = 8 Hz, 4H, Ar).
1b ($CDCl_3$): 1.05 (d, J = 7 Hz, 6H, 2 x CH_3CH), 2.4 (s, 3H, CH_3Ar), 3.9 (m, 1H, CH), 4.1 (s, 2H, CH_2S), 5.5, 5.9 (2 s, 2H, CH_2=C), 6.3 (d, J = 7 Hz, 1H, NH), 7.3, 7.7 (2 d, J = 8 Hz, 4H, Ar).
3a: 1.2 (d, J = 7 Hz, 6 H, 2 x CH_3CH), 3.0 (d, J = 7 Hz, 2 H, CH_2CH), 4.0 (m, 1H, CHN), 4.7-6.1 (m with 2 s at 5.15 and 5.6, 5H, 2 x CH_2C and CH=C), 6.4 (br s, 1H, NH).
3b: 0.9 (t, J = 7 Hz, 3H, CH_3CH_2), 1.15 (d, J = 7 Hz, 6H, 2 x CH_3CH), 1.45 (m, 2H, CH_2CH_3), 2.2 (t, J = 7 Hz, 2H, CH_2C=C), 4.0 (m, 1H, CHN), 5.1, 5.45 (2 s, 2H, CH_2=C), 6.5 (br s, 1H, NH).
3c: 1.15 (d, J = 7 Hz, 6H, 2 x CH_3CH), 2.25 (m, 4H, CH_2CH_2C=C), 4.0 (m, 1H, CHN), 4.5-5.3 (m with s at 5.1, 3H, CH_2=CH and CH=C), 5.3-6.1 (m with s at 5.45, 2H, CH=CH_2 and CH=C), 6.4 (br s, 1H, NH).
3d: 0.9 (deformed t, 3H, CH_3CH_2), 1.3 (m, 6H, 3 x CH_2), 2.25 (t, J = 7 Hz, 2H, CH_2C=C), 3.7 (s, 3H, CH_3O), 5.4, 6.0 (2 s, 2H, CH_2=C).
3e: 3.5 (s, 2H, CH_2Ph), 3.65 (s, 3H, CH_3O), 5.3, 6.1 (2 s, 2H, CH_2=C), 7.1 (s, 5H, Ph).
3f: 1.05 (d, J = 7 Hz, 6H, 2 x CH_3CH), 3.5 (s, 2H, CH_2Ph), 3.95 (m, 1H, CHN), 5.0, 5.6 (2 s, 2H, CH_2=C), 6.65 (br s, 1H, NH), 7.1 (s, 5H, Ph).
3g: 1.4 (t, J = 7 Hz, 6H, 2 x CH_3CH_2), 2.75 (br d, J = 8 Hz, 2H, CH_2CH), 3.45 (dd, J = 7 and 8 Hz, 1H, CH), 3.9 (s, 3H, CH_3O), 4.1 (q, J = 7 Hz, 4H, 2 x CH_2O), 5.6, 6.1 (2 s, 2H, CH_2=C).
3h: 1.15 (d, J = 7 Hz, 6H, 2 x CH_3CH), 1.25 (t, J = 7 Hz, 6H, 2 x CH_3CH_2), 2.75 (br d, J = 8 Hz, 2H, CH_2CH), 3.6 (dd, J = 7 and 8 Hz, 1H, $CHCH_2$), 4.1 (m with a q, J = 7 Hz, 5H, 2 x CH_2O and CHN), 5.25, 5.55 (2 s, 2H, CH_2=C), 6.6 (br s, 1H, NH).
12. We thank the University of Alicante for financial assistance.
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