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(E)-N-ISOPROPYL-3-TOSYLACRYLAMIDE: A NEW α-ACYLVINYL CATION EQUIVALENT IN THE SYNTHESIS OF α-SUBSTITUTED ACRYLAMIDES

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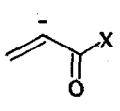
Summary: The reaction of (E)-N-isopropyl-3-tosylacrylamide with different Grignard reagents leads after hydrolysis to the corresponding α-alkylated systems **7**, which by treatment with methanolic potassium hydroxide yield the expected α-methylene amides **8**. In the case of using vinylmagnesium bromide the aqueous hydrolysis after the first step affords directly mikanecic acid diisopropylamide **11**. When sodium diethyl malonate is used as nucleophile the corresponding succinimide derivatives **13** and **14** are isolated.

α-Substituted acrylates are mainly prepared using (a) the acrylate moiety as an α-acylvinyl carbanion **1**[1] or its equivalents, such as **2**[2] or **3**[3] and (b) the methacrylate moiety as cationic,[4] radical,[5] or anionic[6] allylic synthons **4**. However, the use of acrylates as α-acylvinyl cations or their equivalents in the synthesis of α-substituted acrylates is in our hands unknown. These synthons **5** are interesting intermediates because they present umpoled reactivity;[7] however, they are rare species due to the fact that in the reaction with nucleophiles such as organometallics they can react at the cationic centre or at the α,β-unsaturated carbonylic functionality.



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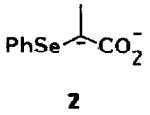

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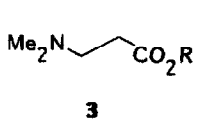

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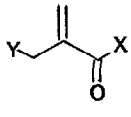

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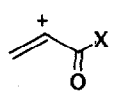

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Following our studies on β-substituted vinyl sulfones acting as β-acylvinyl anionic[8] or cationic[9] intermediates we report here the use of the easily available (E)-N-isopropyl-3-tosylacrylamide **6**[9a] as an α-acylvinyl cation equivalent of the type **5**.

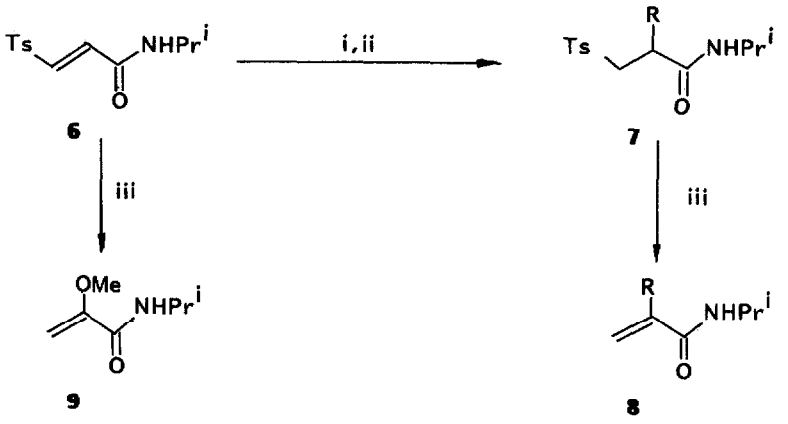
When (E)-N-isopropyl-3-tosylacrylamide (**6**) was treated with two equivalents of an organomagnesium compound at -15°C in tetrahydrofuran products **7** were regioselectively obtained. The treatment of compounds **7**[10] with a 1N solution of potassium hydroxide in methanol afforded α-methylene amides **8** (Scheme 1 and Table 1). Compound **6** also reacts with methanolic potassium hydroxide to give the piruvic amide derivative **9**[11] (80% yield) resulting from the Michael addition of the methoxide anion followed by elimination of the p-toluenesulfinate group.

Table 1. Reaction of (E)-N-isopropyl-3-tosylacrylamide **6** with carbanionic reagents and subsequent elimination reaction. Synthesis of compounds **7**, **8**, and **10-14**.

Organometallic	Products **7** and **13**[a]			Products **8** and **10-14**[a]			
	No.	Yield(%)[b]	M.p.(°C)[c]	No.	Reaction time	Yield(%)[d]	M.p.(°C)[c] or R_f[e]
EtMgBr	**7a**	81	139-140	**8a**	1 d	58	0.50
CH_2=CHMgBr	**7b**	94	128-129	**8b**[f]	1 d	95[g]	0.46
				10	1 d	90	0.33
				11[h]	15 min	90	179-180
CH_2=$CHCH_2$MgBr	**7c**	84	118-119	**8c**	1 d	81	0.53
				12	1 h[i]	78	0.48
Bu^nMgBr	**7d**	77	112-113	**8d**	1 d	74[j]	0.61
PhMgBr	**7e**	92	150-151	**8e**	5 h	78	0.50
$NaCH(CO_2Et)_2$[k]	**13**	95	108-109[l]	**14**	10 min	73	0.61

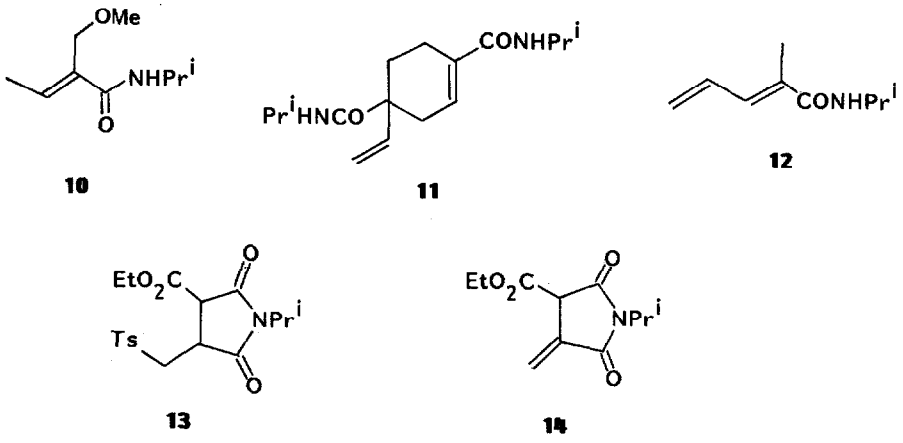
[a] All compounds gave satisfactory spectral data (i.r., ^{1}H n.m.r., and mass spectra) and analytical data. [b] Isolated crude yield based on compound **6**; these products were homogeneous (t.l.c.) and pure (>90%, n.m.r.). [c] Dichloromethane/hexane. [d] After column chromatography on silica gel; based on compound **6**. [e] Hexane/ethyl acetate: 1/1. [f] The elimination reaction was carried out with 1 N aqueous sodium hydroxide in tetrahydrofuran. [g] Crude yield of homogeneous (t.l.c.) and pure (>90%, n.m.r.) product. [h] The reaction mixture was quenched with water. [i] Reflux time for the starting compound **8c**. [j] Based on compound **7d**. [k] One equivalent of sodium diethyl malonate was used. [l] Hexane/ether.

In the specially interesting case of vinylmagnesium bromide the unstable dienic compound **8b** suffers conjugated addition of the methoxide anion to yield stereoselectively compound **10**. The in situ hydrolysis of **7b** with water gave after 15 min mikanecic acid diamide **11**[12,13] resulting from a spontaneous Diels-Alder reaction[12,14] of compound **8b**; this route represents a convenient way for mikanecic acid derivatives.[12,13] When compound **7b** was treated with 1 N aqueous sodium hydroxide in tetrahydrofuran the monomer **8b** could be obtained in ethereal solution after extractive work-up (Table 1); this procedure for **8b** allows its use in Diels-Alder reactions.[12,15] The allylmagnesium derivative **8c** isomerizes to the dienamide **12** when the elimination with methanolic potassium hydroxide was carried out under reflux.

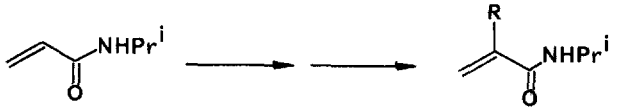


Scheme 1. Reagents: i, 2 RMgBr; ii, HCl-H_2O; iii, KOH-MeOH.

Sodium diethyl malonate[16] reacts with the starting material **6** to give the succinimide derivative **13**, which after alkaline treatment as above affords compound **14**. Compound **13** results from an intramolecular cyclization of the initially formed product **7**.



We can conclude that (E)-N-isopropyl-3-tosylacrylamide is an interesting α-acylvinyl cationic equivalent synthetically usefull in the preparation of α-methylene amides. Since the starting material **6** is easily prepared from the corresponding acrylamide[9] the study described in this paper allows the stepwise following transformation, the rest R being a carbanionic group (Scheme 2).



Scheme 2.

In a typical reaction an ethereal solution of the Grignard reagent (2.2 mmol) or sodium diethyl malonate[17] (1.1 mmol) was added to a solution of (E)-N-isopropyl-3-tosylacrylamide **6** (267 mg, 1 mmol) in tetrahydrofuran (5 ml) at -15°C. The reaction mixture was stirred for 5 h at room temperature, hydrolyzed with aqueous 1 N hydrochloric acid[18] and extracted with dichloromethane. The organic layer was washed with water, dried over anhydrous sodium sulfate, and evaporated (15 torr) to afford crude products **7** and **13**, which were purified by recrystallization to be fully characterized. Crude products **7** and **13** were treated with 1 N methanolic potassium hydroxide for 10 min to 1 d (see Table 1). The resulting solution was evaporated (15 torr) and the residue was dissolved in water and extracted with ether. The organic phase was dried over anhydrous sodium sulfate and evaporated (15 torr) to yield crude products **8** and **10-14**, which were purified by column chromatography on silica gel.[19,20]

References and Notes

1. See, for instance: (a) B. A. Feit, U. Melamed, R. R. Schmidt, and H. Speer, J. Chem. Soc., Perkin Trans. 1, **1981**, 1329; (b) S. E. Drewes and G. H. P. Roos, Tetrahedron Lett., **1988**, 44, 4653.
2. N. Petragnani and H. M. C. Ferraz, Synthesis, **1985**, 27.
3. L. C. Yu and P. Helquist, J. Org. Chem., **1981**, 46, 4536 and references cited therein.
4. C. Nájera, B. Mancheño, and M. Yus, Tetrahedron Lett., **1989**, in the press.
5. J. E. Baldwin, R. M. Adlington, D. J. Birch, J. A. Crawford, and J. B. Sweeney, J. Chem. Soc., Chem. Commun., **1986**, 1339.
6. (a) K. Tanaka, H. Horiuchi, and H. Yoda, J. Org. Chem., **1989**, 54, 63; (b) P. Beak and D. A. Burg, J. Org. Chem., **1989**, 54, 1647 and references cited therein.
7. (a) D. Seebach, Angew. Chem., **1979**, 91, 259; Angew. Chem. Int. Ed. Engl., **1979**, 18, 239; (b) T. A. Hase, "Umpoled Synthons", J. Wiley & Sons, New York, 1987.
8. (a) C. Nájera and M. Yus, Tetrahedron Lett., **1987**, 28, 6709; (b) C. Nájera and M. Yus, J. Org. Chem., **1988**, 53, 4708; (c) C. Nájera and M. Yus, J. Org. Chem., **1989**, 54, 1491; (d) C. Nájera and M. Yus, J. Chem. Soc., Perkin Trans. 1, **1989**, in the press.
9. (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.
10. This type of compounds has been used in the synthesis of butenolides: K. Tanaka, H. Wakita, H. Yoda, and A. Kaji, Chem. Lett., **1984**, 1359.
11. R. R. Schmidt, A. Euhsen, and R. Betz, Synthesis, **1985**, 160.
12. The corresponding acid has been recently obtained from the dimer of 2-cyano-1,3-butadiene by acid hydrolysis: P. G. Baraldi, A. Barco, S. Benetti, S. Manfredini, G. P. Pollini, D. Simoni, and V. Zanirato, Tetrahedron, **1988**, 44, 6451.
13. Mikanecic acid was isolated from the alkaloids mikanoidine and sarracine. For synthetic studies see: H. M. R. Hoffmann and J. Rabe, Helv. Chim. Acta, **1984**, 67, 413 and references cited therein.
14. This spontaneous dimerization has been also observed in the case of ketones derivatives: H. M. R. Hoffmann, U. Eggert, and W. Poly, Angew. Chem., **1987**, 99, 1047; Angew. Chem. Int. Ed. Engl., **1987**, 26, 1015.
15. For reactions of this type see, for instance: J.-E. Bäckvall and S. K. Juntunen, J. Am. Chem. Soc., **1987**, 109, 6396 and references cited therein.
16. This Michael type addition has been also observed with (E)-N-(3-tosylacryloyl)piperidine and (E) ethyl 3-tosylacrylate: see reference 9b.
17. Prepared from diethyl malonate and sodium hydride in tetrahydrofuran.
18. In the case of mikanecic acid diisopropylamide **11** the reaction mixture was quenched with water and stirred for 15 min.
19. Compound **8b** dimerizes under these conditions to afford product **11**.

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