Synthesis and Properties of 4,*N*-Dimethyl-*N*-(3-oxo-4-pentenyl)benzenesulfonamide, a Divinyl Ketone Equivalent

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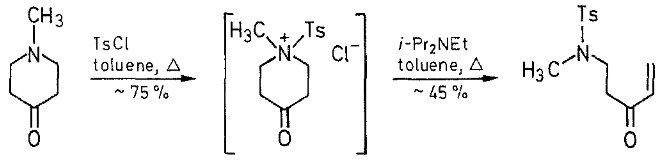
Starting from 1-methyl-4-piperidone, some synthetically useful Michael adducts of divinylketone were prepared and characterized.

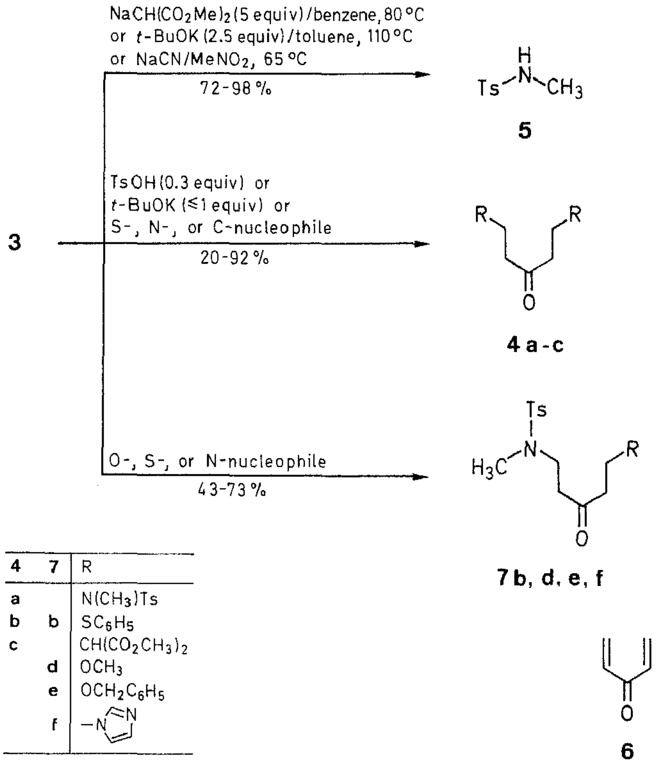
In the course of a study aimed at the synthesis of nitrogen-containing vinyl ketones we found that exposure of the salt **2** obtained from 1-methyl-4-piperidone (**1**) and tosyl chloride to the action of strong bases gave rise to 4,*N*-dimethyl-*N*-(3-oxo-4-pentenyl)benzenesulfonamide (**3**), 1,5-bis(methyltosylamino)-3-pentanone (**4a**), or 4,*N*-dimethylbenzenesulfonamide (**5**), depending on the reaction conditions.

The presence of two tosylamino groups in compound **4a** as well as the formation of 4,*N*-dimethylbenzenesulfonamide (**5**)[2] clearly indicated that the two C-N bonds of the salt **2** had been successively cleaved. Compounds **3** and **4a** can be considered as the mono- and the bis-adduct, respectively of **5** with divinyl ketone (**6**). Since divinyl ketone (**6**) proved to be an interesting synthon for the preparation of natural products[3] and also because some bis β-aminoketones (similar to the bis(tosylamide) **4a**) have been shown to display antitumor activities,[4] we attempted to prepare symmetrical **4** and unsymmetrical **7** Michael adducts of divinyl ketone (**6**), starting from ketone **3**.

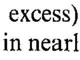
N-Sulfonylation of 1-methyl-4-piperidone (**1**) with a small excess of tosyl chloride led to the quaternary salt **2** in 75% yield (determined by the integral of the NMR signals of the protons at C-2 and C-5). Ring opening of **2** was performed by the action of Hunig's base (ethyldiisopropylamine) in toluene at 100 °C. The only moderate yield of ketone **3** (34% based on **1**) may result from the high reactivity of **3** towards basic reagents.

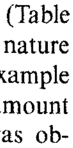


1 **2** **3** 30% (based on **1**)



7b, d, e, f

4	7	R
a		N(CH$_3$)Ts
b	b	SC$_6$H$_5$
c		CH(CO$_2$CH$_3$)$_2$
	d	OCH$_3$
	e	OCH$_2$C$_6$H$_5$
	f	



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Three compounds (**4a–c**) were obtained from the reaction of representative N-, S-, and C-nucleophiles with ketone **3** (Table 1). The course of the reactions mostly depended on the nature and on the relative amount of the reagent used. For example with potassium *tert*-butoxide used in stoichiometrical amount (or in excess), 4,*N*-dimethylbenzenesulfonamide (**5**) was obtained in nearly quantitative yield, whereas the other part of the molecule (divinyl ketone **6**) could not be detected as such (entry 1).

The same result was obtained with basic C-nucleophiles like dimethyl sodiomalonate (entry 2) or sodium cyanide (entry 3). On the other hand, when potassium *tert*-butoxide was used as catalyst, the rate of C-N bond cleavage of **3** decreased, the resultant sulfonamide **5** reacted with **3** to afford the bis-sulfonamide **4a**, in the absence (entry 4) and even in the presence of a large excess of nucleophiles (entry 5). A better yield of **4a** was obtained when the preformed sulfonamide **5**[5] was added to the reaction mixture (entry 6).

Considering that free divinyl ketone (**6**) was not necessarily involved in the formation of products **4**, we sought reaction conditions which would allow the rate of the Michael addition to be comparable with that of the C-N cleavage: for example, 1,5-bis(phenylthio)-3-pentanone (**4b**) was directly obtained upon reaction of **3** with potassium benzenethiolate (entry 7), and tetramethyl 3-oxo-1,5-pentanediylbis(malonate) (**4c**) could be prepared with dimethyl malonate and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, entry 8). In the *p*-toluenesulfonic acid catalyzed reaction, compound **3** was directly converted into **4a** (entry 9).

Examination of the Michael addition of various nucleophiles to **3** revealed that carbanions like cyanide (entry 3) or malonate (entry 2) afforded only the cleaved product **5**. Better results were obtained with alcohols (entry 13) and alkoxides (entry 11), with benzenethiol (entry 12), or with imidazole (entry 14).

While the extreme lability of the C-N bond of **3** towards basic nucleophiles hampers the easiness of these reactions and implies careful choice of the experimental conditions, it remains that the vinyl ketone **3** can be considered as a suitable precursor for various new, synthetically useful 1,5-dihetero-substituted 3-pentanones (**4**,**7**).

All reagents were purchased from Aldrich Chemical Co., and were used without purification, except for 1-methyl-4-piperidone which was redistilled before use. Kieselgel F_{254} GH Merck was used for chromatographic separation.

4,*N*-Dimethyl-*N*-(3-oxo-4-pentenyl)benzenesulfonamide (3):
1-Methyl-4-piperidone (**1**; 0.34 g, 3.0 mmol) in toluene (3 mL) and TsCl (0.76 g, 4.0 mmol) dissolved in toluene (3 mL) are maintained at 100 °C under argon. After 1 h, *i*-Pr_2NEt (0.52 g, 0.4 mmol), 0.70 mL) is added and the heating of the mixture is continued for 0.5 h. The solvent is removed *in vacuo*, the residue dissolved in CH_2Cl_2 (10 mL), this solution basified with 10% aqueous $NaHCO_3$, and the organic layer separated. The aqueous layer is extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic phases are dried ($MgSO_4$). Evaporation of the solvent followed by purification using centrifugal chromatography (Chromatotron®), (silica gel, CH_2Cl_2) affords compound **3**; yield: 0.33 g (30%). mp 39 °C; recovered starting material **1**: 0.09 g (11%); yield of **3** based on converted starting material: 34%.

Table 1. Preparation of Symmetrical (**4**) and Unsymmetrical (**7**) Ketones

Entry	Nucleophile (mole equiv)	Condensing Agent (mole equiv)	Reaction Time (h)	Temperature (°C)	Product	Yield[a] (%)	Remarks
1	none	*t*-BuOK (2.5)	2	110	**5**	91	solvent : toluene
2	$NaCH(CO_2CH_3)_2$ (5)	none	2	80	**5**	72	solvent : benzene
3	NaCN	none	2	65	**5**	98	solvent : MeCN
4	none	*t*-BuOK (0.3)	1	80	**4a**	26[b]	
5	$CH_2(CO_2CH_3)_2$ (10)	*t*-BuOK (0.1)	0.5	20	**4a**	22[b]	
6	$4\text{-}CH_3C_6H_4SO_2NHCH_3$ (4)	*t*-BuOK (1)	0.5	80	**4a**[c]	92	
7	C_6H_5SK (15)	none	0.5	80	**4b**[c]	37	
8	$CH_2(CO_2CH_3)_2$ (5)	DBU (3)	0.5	80	**4c**	47	
9	none	TsOH (0.3)	3	80	**4a**	29[b]	8% of **3** unreacted
10	$CH_2(CO_2CH_3)_2$ (6)	$(C_2H_5)_3N$ (2)	17	80	none	–	see also Entries 2,5
11	CH_3OH (solvent)	MeONa (0.3)	0.5	64	**7d**[c]	50	neat, 14% of **5**
12	C_6H_5SH (10)	none	0.25	80	**7b**	60	
13	$C_6H_5CH_2OH$ (15)	TsOH (0.1)	1	80	**7e**	43	28% of **4a**
14	imidazole (5)	none	16	20	**7f**	73	

[a] Obtained after TLC.

[b] In these cases, the theoretical yield does not exceed 50%.

[c] Prepared on a 2.5–3 mmol scale.

Table 2. Compounds **3**, **4**, and **7** Prepared

Compound[a]	mp (°C)[b] or bp (°C) or n_D^{22}	Molecular Formula[c]	MS (70 eV)[d] *m/z* (%)	Exact Mass[d] *m/z*
3	39	$C_{13}H_{17}NO_3S$ (267.3)	267 (31), 210 (28), 198 (98), 186 (31), 155 (98), 151 (63)	$(M+H)^+$ calc. 268.1005 found 268.0979
4a	73–74	$C_{21}H_{28}N_2O_5S_2$ (452.6)	452 (1), 297 (57), 198 (94), 155 (100), 112 (71), 93 (98)	$M^{+\cdot}$ calc. 452.1438 found 452.1413
4b	243–247/1100 mbar	$C_{17}H_{18}OS_2$ (302.4)	302 (66), 193 (42), 165 (10), 137 (40), 123 (100), 109 (61)	$M^{+\cdot}$ calc. 302.0799 found 302.0827
4c	1.4643	$C_{15}H_{22}O_9$ (346.3)	346 (98), 187 (43), 159 (37), 155 (100)	$(M+H)^+$ calc. 346.1262 found 346.1197
7b	1.5702	$C_{19}H_{23}NO_3S_2$ (377.5)	377 (11), 279 (4), 268 (2), 259 (13), 218 (17)	$M^{+\cdot}$ calc. 377.1119 found 377.1139
7d	1.5252	$C_{14}H_{21}NO_4S$ (299.4)	299 (1), 268 (1), 198 (11), 185 (20), 155 (40), 144 (32)	$(M+H)^+$ calc. 300.1269 found 300.1274
7e	1.5494	$C_{20}H_{25}NO_4S$ (375.5)	376 (96), 268 (57), 220 (90), 198 (86), 155 (21)	$(M+H)^+$ calc. 376.1582 found 376.1618
7f	1.5415	$C_{16}H_{21}N_3O_3S$ (335.4)	335 (2), 267 (0.4), 198 (11), 185 (17), 180 (23), 155 (62)	$(M+H)^+$ calc. 336.1382 found 336.1393

[a] All new compounds.

[b] Uncorrected, measured with a Kofler apparatus.

[c] Satisfactory microanalyses obtained: C ±0.37, H ±0.32, N ±0.47, S +0.50.

[d] Recorded on a JEOL JMS D300 high-resolution spectrometer.

Table 3. Spectral Data of Compounds **3**, **4**, and **7**

Compound	IR (film)[a] ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/300 MHz)[b] δ, J(Hz)	^{13}C-NMR ($CDCl_3$/75 MHz)[b] δ
3	1690, 1670, 1660	2.33 (s, 3H, $ArC\underline{H}_3$); 2.68 (s, 3H, NCH_3); 2.87 (t, 2H, $J = 7$, $COCH_2$); 3.24 (t, 2H, $J = 7$, NCH_2); 5.81 (dd, 1H, $J_1 = 10$, $J_2 = 1$, $CO{-}CH{=}C\underline{H}_{trans}$); 6.16 (d, d, 1H, $J_3 = 18$, $J_2 = 1$, $CO{-}CH{=}C\underline{H}_{cis}$); 6.27 (d, d, 1H, $J_1 = 10$, $J_3 = 18$, $CO{-}C\underline{H}{=}CH_2$	21.5; 36.1; 38.7; 45.5; 127.4; 129.1; 134.3; 136.3; 143.5; 198.6
4a	1705	2.36 (s, 6H, $2ArC\underline{H}_3$); 2.67 (s, 6H, $2NCH_3$); 2.73 (t, 4H, $J = 7$, $2CH_2CO{-}$); 3.18 (t, 4H, $J = 7$, NCH_2); 7.26 (d, 4H, $J = 8$, H_{arom}); 7.58 (d, 4H, $J = 8$, H_{arom})	21.6; 36.1; 42.3; 45.4; 127.6; 129.9; 134.2; 143.7; 206.6
4b	1710	2.70 (t, 4H, $J = 7$, $COC\underline{H}_2$); 3.12 (t, 4H, $J = 7$, $C\underline{H}_2SC_6H_5$); 7.16–7.52 (m, 10 H_{arom})	27.5; 42.5; 126.4; 129.0; 129.7; 136.4; 206.7
4c	1750, 1730, 1710	2.18 [t, 4H, $J = 7$, $C\underline{H}_2CH(CO_2CH_3)_2$]; 2.51 (t, 4H, $J = 7$, $COCH_2$); 3.43 [t, 2H, $J = 7$, $CH_2C\underline{H}(CO_2CH_3)_2$]; 3.74 (s, 12H, OCH_3)	22.6; 39.7; 50.5; 52.7; 169.6; 207.6
7b	1710	2.42 (s, 3H, $ArC\underline{H}_3$); 2.72 (d, 2H, $J = 7$, $COC\underline{H}_2CH_2SC_6H_5$); 2.73 (s, 3H, NCH_3); 2.75 (t, 2H, $J = 7$, $COC\underline{H}_2CH_2N$); 3.13 (t, 2H, $J = 7$, $C\underline{H}_2SC_6H_5$); 3.27 (t, 2H, $J = 7$, $COCH_2C\underline{H}_2N$); 7.18–7.67 (m, 9 H_{arom})	21.4; 27.4; 36.0; 42.2; 42.4; 45.1; 126.4; 127.4; 129.0; 129.6; 129.7; 134.1; 135.4; 143.5; 206.7
7d	1710	2.42 (s, 3H, $ArC\underline{H}_3$); 2.68 (t, 2H, $J = 7$, $COC\underline{H}_2CH_2N$); 2.74 (s, 3H, $NC\underline{H}_3$); 2.81 (t, 2H, $J = 7$, $COC\underline{H}_2CH_2OCH_3$); 3.27 (t, 2H, $J = 7$, NCH_2); 3.32 (s, 3H, $OC\underline{H}_3$); 3.64 (t, 2H, $J = 7$, $C\underline{H}_2OCH_3$); 7.33 (d, 2H, $J = 8_{arom}$); 7.67 (d, 2H, $J = 8_{arom}$)	21.4; 35.9; 42.4; 43.0; 45.1; 58.8; 67.3; 127.4; 129.7; 134.2; 143.4; 207.1
7e	1710	2.42 (s, 3H, $ArC\underline{H}_3$); 2.71 (t, 2H, $J = 7$, $COC\underline{H}_2CH_2N$); 2.73 (s, 3H, NCH_3); 2.80 (t, 2H, $J = 7$, $COC\underline{H}_2CH_2OCH_2{-}$); 3.26 (t, 2H, $J = 7$, NCH_2); 3.74 (t, 2H, $J = 7$, $COCH_2C\underline{H}_2O$); 4.49 (s, 2H, $OC\underline{H}_2C_6H_5$); 7.17–7.35 (m, 7 H_{arom}); 7.64 (d, 2H, $J = 8\,H_{arom}$)	21.6; 36.0; 42.5; 43.3; 45.2; 65.2; 73.3; 127.3; 127.5; 127.8; 128.5; 129.6; 134.3; 138.1; 143.6; 207.3
7f	1710, 1600	2.43 (s, 3H, $ArC\underline{H}_3$); 2.71 (s, 3H, $NC\underline{H}_3$); 2.73 (t, 2H, $J = 7$, $COC\underline{H}_2CH_2NSO_2$); 2.97 (t, 2H, $J = 7$, $COC\underline{H}_2CH_2$-imidazolyl); 3.24 (t, 2H, $J = 7$, $COCH_2C\underline{H}_2NSO_2$); 4.23 (t, 2H, $J = 7$, $C\underline{H}_2$ imidazolyl); 6.97 (d, 2H, $J = 32$, $C\underline{H}{=}C\underline{H}$); 7.33 (d, 2H, $J = 8\,H_{arom}$); 7.49 (s, 1H, $NCH{=}N$); 7.65 (d, 2H, $J = 8\,H_{arom}$)	21.4; 36.1; 40.8; 42.3; 43.8; 45.2; 116.7; 127.3; 129.5; 129.7; 133.8; 143.6; 205.4

[a] Recorded on a Beckmann Acculab 4 spectrophotometer.

[b] Obtained on a Brucker AC300 spectrometer using TMS as internal standard.

Symmetrical (4) and Unsymmetrical (7) Ketones; General Procedure:
A solution of ketone **3** (53.5 mg, 0.2 mmol) in benzene (except entries 1, 3, 11; see Table 1, remarks) is stirred with the nucleophile under the conditions listed in Table 1. When TLC shows the disappearance of the starting material, the solvent is removed under reduced pressure. The residue is dissolved in CH_2Cl_2 (5–10 mL), this solution is neutralized with 10% aqueous NaOAc, and the aqueous layer is further extracted with CH_2Cl_2 (3×10 mL). The combined organic layers are dried ($MgSO_4$), the solvent is evaporated, and the residue is purified by TLC on silica gel using CH_2Cl_2 as eluent.

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