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REACTION OF *p*-TOLUENESULFONYL ISOCYANATE WITH ELECTRON-RICH ALKENES AND MONOFLUOROALKENES

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Abstract

Mild neat reactions of p-toluenesulfonyl isocyanate (1) with electron-rich alkenes and monofluoroalkenes give [2 + 2] cycloaddition products without opening the beta-lactam ring. Reaction of 1 with the very reactive alkene 3,4-dihydro-2H-pyran at 0 °C or below in solution gives an intact [2 + 2] product. Line-broadening of TMS was found during the reaction of 3,4-dihydro-2H-pyran with 1 in $CDCl_3$ indicating a 1,4-diradical intermediate from a Single Electron Transfer (SET) pathway.

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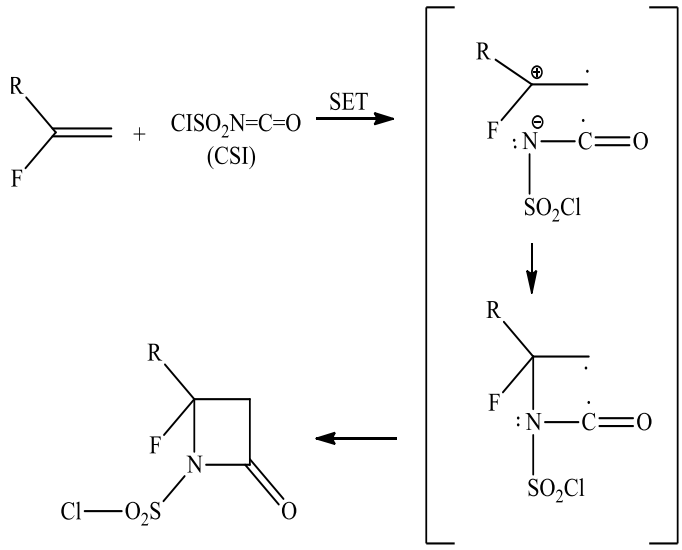
Introduction

The β-lactam ring is found in some antibacterial reagents (1) and potential cholesterol-lowering drugs (2). β-Lactams are precursors to ring-opened compounds (3-7) and derivatives from the β-lactams are prepared from nitrogen (8) and oxygen alkylations (4,9) on the four-membered ring. In previous studies we treated chlorosulfonyl isocyanate (CSI) with monofluoroalkenes to give β-lactams with the fluorine on the four membered ring (10-14). The impact of fluorine on new drugs coming to market for human and veterinary use (15-17), along with products for agricultural applications (18-19) has been reported. It is estimated that up to 20% of new pharmaceuticals contain a fluorine in the molecule (17).

Previous studies with (CSI) found that it reacts with electron-deficient alkenes by a concerted pathway (13, 14). Electron-rich alkenes were found to react via a Single Electron Transfer (SET) pathway to give 1,4-diradical intermediates (Scheme 1) (10, 13). The 1,4-diradical intermediates were readily detected in the NMR by line-broadening of an internal standard. We also reported that the Triplet 1,4-diradical can rearrange to the Singlet form at lower temperature (10). Other studies also found that in many cases neat reactions with CSI and alkenes give cleaner reactions and higher product yields than reactions run in solvent (11). Chlorosulfonyl isocyanate is the most reactive isocyanate but it is still a sluggish electrophile (12). In this paper we treat the less reactive p-toluenesulfonyl isocyanate (1) with electron-rich alkenes and monofluoroalkenes under neat mild reaction conditions to investigate the synthetic utility to prepare monofluoro-tosyl-β-lactams. We also study the reaction of 1 with an alkene reactive enough to give a smooth reaction in solution, and thereby determine if 1 reacts via a SET pathway similar to the more reactive CSI (10). There are few reactions reported for [2+2] cycloadditions with 1 since the four-membered ring of the tosyl- β-lactam products open at the higher temperatures required for reaction of this weak electrophile in solution (20-23).



Scheme 1

Experimental

Monofluoroalkenes were synthesized as described previously (10-12). Tosyl-β-lactam products from 3,4-dihydro-2H-pyran (20-23), and methylenecyclohexane (21), are described in the literature.

General procedure for neat reactions: To a dry small round bottom flask fitted with a drying tube and magnetic stirring bar was added 5.0 mmol alkene followed by1,006 mg (5.1 mmol) p-toluenesulfonyl isocyanate (1) and reacted as described below. Work-up: The solid mixture was dissolved with methylene chloride and then added to cold ice water. The aqueous layer was washed three times with methylene chloride and the combined organic extractions washed with 2.5 % aq $NaHCO_3$, then saturated aq. NaCl and dried over anhyd. $NaHSO_4$. The solvent was evaporated and the sample was purified by column chromatography or by chromatography using the auto prep instrument on a 4-gram Silica gel flash column with ethyl acetate /hexanes as the eluant.

1-Tosyl-1-azaspiro[3,5]nonan-2-one (4): The neat reaction mixture of 480 mg methylenecyclohexane and 1,006 mg (5.10 mmol) 1 was stirred at room temperature for 168 hours. Work-up and column chromatography with 70-230 mesh Silica gel gave 1,437 mg (4.89 mmol), a 98 % yield β-lactam 4 for this neat reaction. A slightly lower yield was obtained when product 4 was isolated using the auto prep instrument. mp = 144-145, lit. 144-145 °C (21). IR (ATR) 2947 (m); 2859 (m); 1780 (s); 1594 (m); 1447 (m); 1361 (s); 1342 (m); 1192 (s); 1163 (s); 1143 (s); 1087 (s); 1030 (m); 823 (m). Our NMR's agree with the low field spectra

in the literature (21). ^{1}H, 400 MHz, ($CDCl_3$) δ= 1.20 (brd. s, 3H); 1.52-1.70 (m, 4 H); 2.21 (brd. s, 2H); 2.44 (s, 3 H); 2.74 (s, 2 H); 7.33 (d, J= 8 Hz, 2 H); 7.90 (d, J= 8 Hz, 2 H). ^{13}C, 100 MHz ($CDCl_3$) δ= 21.6; 24.1; 24.4; 35.2; 48.0; 67.6; 127.2; 129.9; 137.5; 144.9; 164.0.

Synthesis and characterization of the unknown tosyl-β-lactam products from alkenes in Table 1 follow.

4-(p-Tolyl)-1-tosylazetidin-2-one (5): The neat reaction mixture containing 590 mg (5.0 mmol) freshly distilled p-methylstyrene and 1,006 mg (5.1 mmol) was heated to 50 °C. Two more equivalent of alkene was added after 10 days to speed up the reaction. Work-up after 20 days at 50 °C and purification as described above with the auto prep gave 952 mg (3.02 mmol) 59 % yield of 5 based on 1 as the limiting reagent. mp 138.8-139.7 °C. IR (ATR) 3010(w); 2930(w); 2910(w); 2840(w); 1790(s); 1597(m); 1361(s); 1256(m); 1167(s); 1135(s); 1090(s); 1018(m); 814(m); 706(m); 674(s). ^{1}H NMR 400 MHz ($CDCl_3$) δ= 2.34 (s, 3H); 2.41(s, 3H); 2.95 (dd, J=16.1 and 3.3 Hz, 1H); 3.44 (dd, J= 16.1 and 6.3 Hz, 1H); 5.03 (dd, J= 6.3 and 3.3 Hz, 1H); 7.09-7.25 (m, 6H); 7.58-7.60 (m, 2H). ^{13}C NMR 100 MHz ($CDCl_3$) δ= 21.2; 21.6; 40.1; 56.6; 126.6; 127.5; 129.4; 129.6; 133.2; 135.8; 138.9; 144.9; 163.8. Exact mass calcd. for [$C_{17}H_{17}NO_3SNa^+$] 338.0821; found 338.0822, Δ= 0.3 ppm.

3,4,4-Trimethyl-1-tosylazetidin-2-one: (6) In a glass sealed pressure tube was added 350 mg (5.0 mmol) 2-methyl-2-butene followed by 1,006 mg (5.10 mmol) 1. The neat reaction was heated for 168 hours at 50 °C. A second equivalent, 350 mg, alkene was then added to speed up the reaction. IR analysis showed the reaction was complete after another 48 more hours at 50 °C. Work-up and purification on the auto prep instrument as described above gave 785 mg (2.94 mmol), 58 % isolated yield of 6 based on 1 as the limiting reagent. mp = 94-96 °C. IR (ATR) 2976 (w); 1772 (s); 1495 (w); 1448 (m); 1351 (s); 1250 (m); 1220 (s); 1185 (m); 1118 (s); 1061 (m); 1006 (s); 940 (m); 828 (m); 724 (m); 706 (m). ^{1}H NMR 400 MHz ($CDCl_3$) δ= 1.15 (d, J= 8 Hz, 3 H); 1.45 (s, 3 H); 1.60 (s, 3H); 2.45 (s, 3H); 2.97 (q, J=8 Hz, 1 H); 7.30-7.382 H); 7.88-7.95 (m, 2H). ^{13}C NMR 100 MHz ($CDCl_3$) δ= 8.85; 21.32; 21.69; 27.06; 54.72; 66.47; 127.28; 129.86; 137.31; 144.90; 167.53. Exact mass calcd. MH^+ for [$C_{13}H_{18}NO_3S$]$^+$ 268.1002; found 268.1008, Δ= 2.2 ppm.

4-Fluoro-4-(p-tolyl)-1-tosylazetidin-2-one (7): The neat reaction mixture of 680 mg (5.0 mmol) α-fluoro-p-methylstyrene and 1,006 mg (5.1 mmol) was heated to 50 °C for 114 hours. Work-up and purification on the auto prep instrument as described above gave 1,130 mg (3.4 mmol) 68 % yield of 7 mp = 123.6-124.7 °C. IR (ATR) 3037(w); 2950(w); 1807(s); 1600(m); 1376(s); 1306(s); 1176(s); 1068(s); 1035(s); 881(s); 671(s). ^{1}H NMR 400 MHz ($CDCl_3$) δ= 2.38 (s; 3H); 2.43 (s, 3H); 3.37 (dd, J= 20.0 and 10.5 Hz, 1H); 3.50 (dd, J= 20.0 and 12.5 Hz, 1H); 7.16-7.37 (m, 6H); 7.66-7.74 (m, 2H). ^{19}F NMR 376 MHz ($CDCl_3$) δ= -128.3 (t, J ~ 10 Hz). ^{13}C NMR 100 MHz ($CDCl_3$) δ= 21.25 (s); 21.72 (s); 53.18 (d, J= 26 Hz); 102.35 (d, J= 240 Hz); 125.06 (d, J= 7 Hz); 127.77 (s); 129.40 (s); 129.77 (s); 131.05 (d, J=30 Hz); 135.77 (s); 140.07 (s); 145.59 (s); 161.42 (d, J= 3 Hz). Exact mass calcd. for [$C_{17}H_{16}FNO_3SNa^+$] 356.0733; found 356.0725, Δ= 2.3 ppm.

4-(4-Chlorophenyl)-4-fluoro-1-tosylazetindin-2-one (8): The neat reaction mixture of 884 mg (2.50 mmol) α-fluoro-p-chlorostyrene followed by 1,006 mg (5.10 mmol) 1 was stirred at 50 °C for 12 days; and then a second equivalent, (884 mg), alkene was added to accelerate the reaction. The mixture was heated at 50 °C for 1 more day. Work-up and purification on the auto prep instrument as described above gave 474 mg (1.34 mmol) 26 % of 8 based on 1 as the limiting reagent. mp = 144-146 °C IR (ATR) 2990 (w); 2929 (w); 2870 (w); 1817 (s); 1597 (m); 1494 (m); 1401 (m); 1375 (m); 1362 (s); 1296 (s); 1193 (s); 1166 (s); 1088 (s); 1070 (s); 1011 (s); 992 (s); 857 (s). ^{1}H NMR 400 MHz ($CDCl_3$) δ= 2.45 (s, 3 H); 3.36 (dd, J= 16.0 and 8.0 Hz, 1 H); 3.54 (dd, J= 16.0 and 8.0 Hz, 3 H); 7.24-7.50 (m,4 H0; 7.67-7.77 (m, 2 H). ^{19}F NMR 376 MHz ($CDCl_3$) δ= -129.04 (t, J~ 10 Hz). ^{13}C NMR,100 MHz ($CDCl_3$) δ= 21.76 (s); 53.21 (d, J= 25 Hz); 101.70 (J= 240 Hz); 126.66 (d, J=8 Hz); 127.77 (s); 129.07 (s); 129.93 (s); 132.64 (d, J= 31 Hz); 135.56 (s); 136.20 (s); 160.91 (s). Exact mass calcd. for [$C_{16}H_{13}ClFNO_3SNa$+] 376.0181; found 376.0188, Δ=1.9 ppm.

4-Fluoro-4-phenyl-1-tosylazetidin-2-one (9): The neat reaction of 305 mg (2.50 mmol) α-fluorostyrene and 500 mg (2.55 mmol) 1 was stirred at 50 °C for 9 days and then another 350 mg alkene was added to speed up the reaction. After 5 more days the reaction was terminated because the product was decomposing faster than formation. Work-up and purification on the auto prep instrument as described above gave red crystals, mp = 80-81 °C, 314 mg (0.982 mmol) of 9, or a 40 % yield based on the amount of 1 that reacted. IR (ATR) 3065(w); 1809 (s); 1597 (m); 1496 (w); 1450 (m); 1372 (s); 1293 (m); 1170 (s); 684 (s); 667 (s); 613 (s). ^{1}H NMR 400 MHz, ($CDCl_3$) δ= 2.42 (s); 3.39 (dd, J= 20 & 10 Hz, 1H); 3.52 (dd, J= 20 & 12 Hz, 1H); 7.23-7.29 (m, 2H); 7.35-7.50 (m, 5H); 7.64- 7.72 (m, 2H). ^{19}F NMR 100 MHz ($CDCl_3$) δ= -128.97. ^{13}C NMR, 100 MHz, ($CDCl_3$) δ= 21.68 (s); 53.12 (d, J= 25 Hz); 102.10 (d, J= 240 Hz); 125.09 (s); 127.66 (s); 128.75 (s); 129.83 (s); 129.90 (s); 133.84 (d, J= 30 Hz); 135.59 (s); 145.71 (s); 161.28 (s). Exact mass calcd. for [$C_{16}H_{14}$ FNO_3SNa^+] 342.0571; found 342.0581, Δ=2.9 ppm.

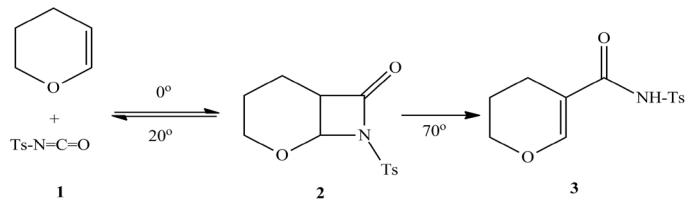
NMR procedure with 3,4-dihydro-2H-pyran to search for the 1,4-diradical intermediate: To a dry NMR tube with 0.5 mL $CDCl_3$ (0.1 % TMS) was added 0.12 mmol alkene. The initial NMR spectrum was expanded from - 0.050 to + 0.050 ppm and recorded. Line-broadened TMS peaks were expanded and recorded about one to two minutes after addition 0.13 mmol 1. The TMS peak returned to its initial peak width at half-height, without shimming, when the reaction was complete.

Results and Discussion

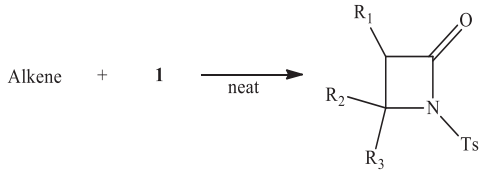
(a) Reaction Utility

Reaction of 1 with the cyclic ether, 3,4-dihydro-2H-pyran, gives the β-lactam (2) at 0 °C (7) which is in equilibrium with 1 and the cyclic ether at room temperature (Scheme 2) (20). Heating 2 in benzene at 70 °C precipitates the α,β-unsaturated amide 3 (20). Hall treated 1 and the cyclic ether in THF at room temperature for 48 hours and isolated 3 in 83 percent yield (22). Our neat reaction of 1 and the cyclic ether at 5 °C gave 2 that was extracted with ether at 0° from the crude mixture after three hours (Table 1). Product 2 crystals decomposed at room temperature.

Scheme 2



Scheme 3



Alkene	Product
Methylene Cyclohexane	**4** R_1 = H; R_2R_3 = spirocyclohexane
p-Methylstyrene	**5** R_1 = R_2 = H; R_3 = *p*-methylstyrene
2-Methyl-2-butene	**6** R_1 = R_2 = R_3 = CH_3
p-Methyl-*alpha*-fluorostyrene	**7** R_1 = H; R_2 = F; R_3 = *p*-methylphenyl
p-Chloro-*alpha*-fluorostyrene	**8** R_1 = H; R_2 = F; R_3 = *p*-chlorophenyl
alpha-Fluorostyrene	**9** R_1 = H; R_2 = F; R_3 = phenyl

Methylenecyclohexane reacts with 1 at room temperature in $CHCl_3$ to give 87 % tosyl-β-lactam, but the reaction takes 4 weeks (Table 1) (21). In nitromethane as solvent, the reaction is complete in 23 hours, but the isolated yield is half of that reported for the slower reaction in $CHCl_3$. The neat reaction of 1 with methylenecyclohexane at room temperature requires only 168 hours at 50 °C to give tosyl-β-lactam 4 with an isolated yield of 98 % (Table 1 and Scheme 3). p-Methylstyrene is the least reactive alkene we studied and it gives poor results in solvent. To speed up the neat reaction of 1 with p-methylstyrene two extra equivalents alkene were added after 10 days. The neat reaction was complete in 20 days at 50 °C with a 59 % isolated yield of 5 (Table 1). 2-Methyl-2-butene reacts in 216 hours with 1 at 50 °C to give 58 % β-lactam 6. The neat reaction of monofluoroalkenes in Table 1 require 50 °C and give moderate to low yields of tosyl-β-fluoro-lactam products.

Table 1
Reaction of p-Toluenesulfonyl Isocyanate (1) with Alkenes and Monofluoroalkenes

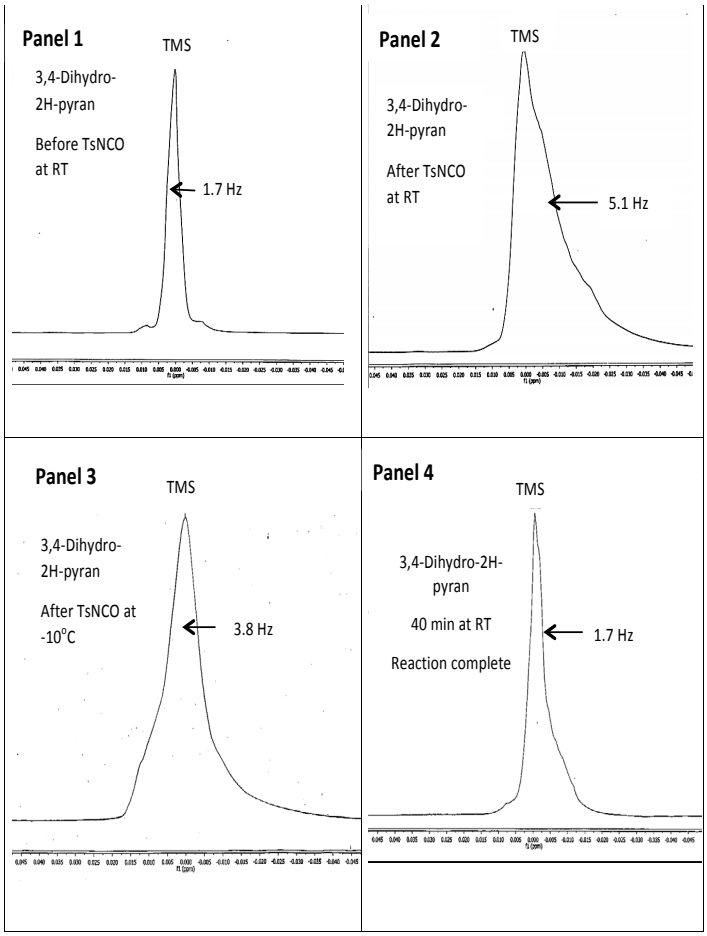
Alkene / Product	Solvent[a] or neat	Temperature (°C)	Reaction Time	Isolated Yield (%)
3,4-Dihydro-2H-pyran / (**2**)	$CDCl_3$	0	1 hr. 40 min.	80[b,c]
	$CDCl_3$	-10	3 hrs.	65[b]
	THF	RT	48 hrs.	83[d] ring-opened product only.
	neat	5	3 hrs.[e]	β-Lactam dec. @ RT
Methylene-cyclohexane / (**4**)	$CHCl_3$	RT	4 weeks	87[c]
	$CDCl_3$	50	6 days	90[f]
	CD_3NO_2	RT	23 hrs	45[f]
	neat	RT	168 hrs	98[g]
p-Methylstyrene / (**5**)	neat	50	20 days	59[h]
	$CHCl_3$	RT	70 hrs	< 5 % reacted[b]
2-Methyl-2-butene / (**6**)	neat	50	216 hrs	58[i]
	neat	RT	Terminated after 20 days	small peak in the IR @ 1772 cm^{-1}
	CH_3NO_2	RT	120 hrs	14[b]
α-Fluoro-*p*-methylstyrene (**7**)	CH_3NO_2	50	dec	na
	neat	50	114 hrs	68[g]
α-Fluoro-*p*-chlorostyrene (**8**)	CH_3NO_2	50	66 hrs	< 10 % reacted
	neat	50	13 days	26[g]
	neat	RT	Terminated after 13 days	small peak in the IR @ 1810 cm^{-1}
α-Fluorostyrene (**9**)	neat	50	14 days	40[g,j]

[a]Five milliliter of solvent was used for 5.0 m mole reactions. [b]Yield by ^{1}H NMR with cyclohexane as internal standard. [c]Barrett , A. G. M.; Betts, M. J.; Fenwick, A.; *J. Org. Chem.*, **1985**, 50(2), 169-175. [d]Chan, J. H. and Hall, S. S.; *J. Org. Chem.* **1984**, 49(1), 195-197. [e]Reaction terminated after 3 hours because ring-opening was faster than β-lactam formation. [f]Yield by ^{1}H NMR with 1,2-dichloroethane as internal standard. [g]Isolated Yield. [h]Two more equivalent of alkene added after 10 days to speed up the reaction. Isolated yield based on the ~ 5.1 m mole isocyanate reacted. [i]A second equivalent alkene was added after 168 hours at 50 °C. [j]Reaction stopped before completion after 14 days because ring-opening was faster than β-lactam formation. Approximately 50 % of the p-toluenesulfonyl isocyanate reacted in 14 days. The 40 % yield is based on the p-toluenesulfonyl isocyanate that reacted.

(b) Single Electron Transfer Pathway

Recently we reported that reactions of CSI with electron- rich alkenes procede via a Single Electron Transfer (SET) pathway (10-13). We found that measuring Line-Broadening by NMR in

Figure 1
Line-Broadening of TMS with Tosyl-isocyanate and the cyclic ether 3,4-Dihydro-2H-pyran.[1] Peak width at half-height.



[1]Line-broadening experiments by NMR with 1 and 3,4-dihydro-2H-pyran were done on a 0.50 mmole scale in 0.5 mL $CDCl_3$.

solution of an internal standard in the reaction was more effective than using TEMPO for detecting di-radicals (10,13). The weaker electrophile 1 was treated with the reactive cyclic vinyl ether 3,4-dihydro-2H-pyran to determine if a 1,4-diradical intermediate was also formed in this reaction. 3,4-Dihydro-2H-pyran was chosen as the alkene for this study since it reacts smoothly to give β-lactam product with 1 in solution at room temperature and at – 10 °C.

At room temperature Line-Broadening of the internal standard TMS was found for the reaction of p-toluenesulfonyl isocyanate (1) with 3,4-dihydro-2H-pyran (Figure 1, compare panels 1 & 2). Line-Broadening did not disappear at lower temperatures (compare panels 1 & 3). We found that lowering the reaction temperature to -10 °C (panel 3) was not sufficient to inhibit line-broadening of TMS. Thus at - 10 °C the intermediate from 1 and 3,4-dihydro-2H-pyran did not convert to the Singlet form at a lower temperature as reported for reactions with (CSI) (10). When the reaction was complete the line-width of the internal standard returns to the value recorded before addition of the electrophile 1 confirming that shimming was not lost during the experiment (compare panels 1 & 4, Figure 1).

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