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Potassium *tert*-Butoxide Catalyzed Addition of Carbonyl Derivatives to Styrenes

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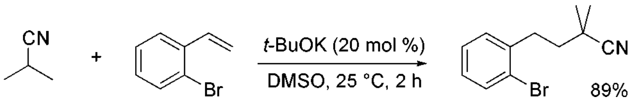
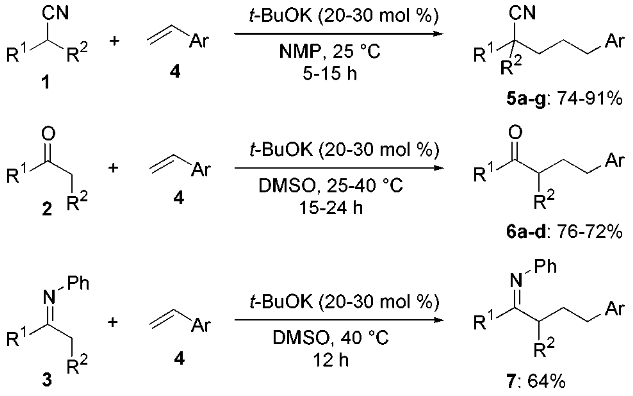
ABSTRACT



A catalytic amount of *t*-BuOK in DMSO allows the addition of ketones or imines to styrenes at 40 °C in good to excellent yield. Nitriles add to styrenes in NMP or in DMSO at room temperature.

The regioselective addition of organometallics to moderately activated olefins such as styrenes is of great importance in polymer chemistry and in carbometalation reactions.[1,2] The scope of these additions is however limited to reactive allylic or alkyl organometallics.[2b] Scarce reports on these reactions can be found in the literature, and only the base-catalyzed addition of cyclic amides to styrene has been reported.[3,4] Recently, we found that highly reactive cesium and potassium alkoxides in *N*-methylpyrrolidinone (NMP) allow the performance of catalytic addition reactions to alkynes.[5] Herein, we wish to report a new general procedure for adding various carbonyl compounds (nitriles (**1**), ketones (**2**), imines (**3**)) to styrenes **4** using a catalytic amount of potassium *tert*-butoxide (10−30 mol %) in dimethyl sulfoxide (DMSO) or NMP leading to the corresponding products **5**−**7** (Scheme 1 and Table 1). The crude reaction mixture is, under optimum conditions, remarkably clean, and the addition products are readily purified. Nitriles are the most reactive substrates, and most reactions are complete at room temperature within 5−15 h in NMP using *t*-BuOK (10−30 mol %) as catalyst, providing the expected regioselective addition products **5a**−**g** in 74−91% yields (see entries 1−7 of Table 1). On the other hand, the presence of an additional substituent at the double

Scheme 1



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[1] (a) For review articles, see: Hoveyda, A. H.; Heron, N. M. In *Comprehensive Asymmetric Catalysis*, Vol. I; Springer: Berlin, 1999; pp 431−454. (b) Marek, I. *J. Chem. Soc., Perkin Trans. 1* **1999**, 535. (c) Knochel, P. In *Comprehensive Organic Synthesis*, Vol. 4; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: Oxford, 1991; p 865.

[2] (a) Priddy, D. B. *Adv. Polym. Sci.* **1994**, *111*, 67. (b) Lemkuhl, H.; McLane, R. *Liebigs Ann. Chem.* **1980**, 736.

[3] (a) Pines, H.; Kannan, S. V.; Simonik, J. *J. Org. Chem.* **1971**, *36*, 2311. (b) For an addition to styrene in the presence of dispersed potassium or sodium, see: Pines, H.; Sartoris, N. E. *J. Org. Chem.* **1969**, 2618.

[4] For the stoichiometric $PdCl_2$-mediated addition of ketones to styrenes, see: Hegedus, L. S.; Williams, R. E.; McGuire, M. A.; Hayashi, T. *J. Am. Chem. Soc.* **1980**, *102*, 4973.

[5] (a) Tzalis, D.; Knochel, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 1463. (b) Tzalis, D.; Koradin, C.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 6193. (c) For a new indole synthesis, see: Rodriguez, A. L.; Koradin, C.; Dohle, W.; Knochel, P. *Angew. Chem., Int. Ed.* In press. (d) Caubere, P. *Chem. Rev.* **1993**, *93*, 2317. (e) Schlosser, M. *Mod. Synth. Methods* **1992**, *6*, 227.

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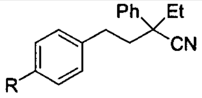
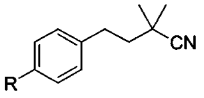
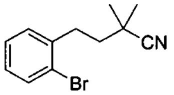
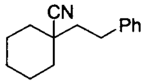
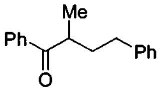
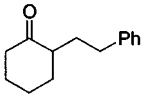
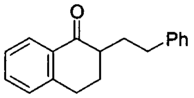
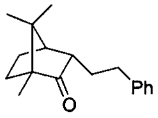
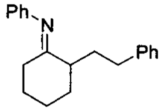
Table 1. Products of Type **5**−**7** Obtained by the Addition of Nitriles, Ketones, or Imines to Styrenes in DMSO or NMP in the Presence of a Catalytic Amount of *t*-BuOK

Entry	Carbonyl compound of type **1-3**			Styrene **4**	Conditions	Product of type **5-7**	Yield
		R^1	R^2	(Ar)	(°C, h)		(%)[a]
1	**1a**	Ph	Et	**4a** : C_6H_5	25, 5	 **5a** : R = H	77[b]
2	**1a**	Ph	Et	**4b** : *p*-F-C_6H_4	25, 5	**5b** : R = F	78[b]
3	**1b**	Me	Me	**4a** : C_6H_5	25, 5	 **5c** : R = H	80[b]
4	**1b**	Me	Me	**4b** : *p*-F-C_6H_4	25, 5	**5d** : R = F	79[b]
5	**1b**	Me	Me	**4c** : *p*-MeO-C_6H_4	25, 15	**5e** : R = OMe	74[b]
6	**1b**	Me	Me	**4d** : *o*-Br-C_6H_4	25, 2	 **5f**	89[c]
7	**1c**	-$(CH_2)_5$-		**4a** : C_6H_5	25, 15	 **5g**	91[b]
8	**2a**	Ph	Me	**4a** : C_6H_5	40, 15	 **6a**	72[c,d]
9	**2b**	-$(CH_2)_4$-		**4a** : C_6H_5	40, 15	 **6b**	60[c,d]
10	**2c**	2-tetralone		**4a** : C_6H_5	40, 15	 **6c**	68[c]
11	**2d**	camphor		**4a** : C_6H_5	40, 24	 **6d**	46[c]
12	**3a**	-$(CH_2)_4$-		**4a** : C_6H_5	40, 12	 **7**	64[c,e]

[a] Yield of analytically pure product was determined by ^1H and ^{13}C NMR. [b] The reaction was performed in NMP (Method A). [c] The reaction was performed in DMSO (Method B). [d] 6−11% of double addition product is isolated. [e] Compound **7a** was converted by acidic hydrolysis to the ketone **6b**.

bond of the styrene, such as (*E*)-1-phenyl-1-butene, requires a reaction temperature of 100 °C (4 h) for completion of the reaction with isobutyronitrile, leading to 3-ethyl-2,2-dimethyl-4-phenylbutanenitrile in 48% yield. The presence of electron-withdrawing substituents such as a fluorine or a bromine group considerably shortens the reaction time (2−5 h instead of 15 h).

The fact that an addition occurs to a 2-substituted styrene seems to indicate that the adding species is not a radical.[6] Moreover, the addition of 2,6-di-*tert*-butyl-4-methylphenol did not inhibit the reaction of **1a** with **4a**. Treatment of 7-phenyl-6-hexenenitrile **8** with *t*-BuOK (30 mol %) in NMP (100 °C, 3 h) furnishes the cyclopentanenitrile **9** in 61% yield

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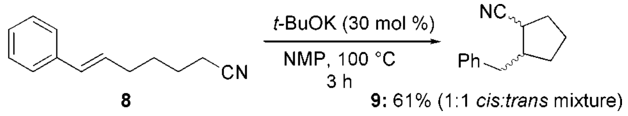
(6) (a) Bunnett, J. F. *Acc. Chem. Res.* **1978**, *11*, 413. (b) Saveant, J. M. *Acc. Chem. Res.* **1980**, *13*, 323. (c) Bunnett, J. F. *Acc. Chem. Res.* **1992**, *25*, 2.

as a 1:1 mixture of cis–trans isomers (Scheme 2). Preliminary experiments show that the amount of *t*-BuOK can be reduced below 10% without a rate decrease.[7]

Scheme 2



In the case of the addition of ketones to styrene, best results were obtained by using DMSO as solvent since it was observed that NMP reacts with styrene.[3a] The reaction temperature is crucial for limiting the formation of double addition products of styrene, and by conducting the reaction between 38 and 41 °C, a smooth addition reaction occurs. In the case of 2-tetralone (**2c**), cyclohexanone (**2b**), and camphor (**2d**), only traces of double addition products were observed and very clean crude reaction mixtures were obtained (entries 8–11 of Table 1). In the case of phenyl ethyl ketone (**2a**), 8% of 1,4-diphenyl-2-methyl-2-(2-phenylethyl)-1-butanone was also isolated. An excess of the ketone (3 equiv) compared to the styrene was used. The addition of imine to styrene could also be achieved at 40 °C, providing the substituted imine **7** in a satisfactory yield.

In summary, we have developed a synthetic method allowing the general addition of carbonyl compounds to styrenes. Furthermore, the combination of *t*-BuOK with the polar solvents DMSO or NMP allows the the reaction to proceed using only a catalytic amount of base. The scope of the reaction appears to be broad and is currently being investigated in our laboratories.

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Supporting Information Available: ^{1}H and ^{13}C NMR data for compounds **5a–g**, **6a–d**, and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[7] **Typical procedure: method A, preparation of 1-(2-phenylethyl)-cyclohexanecarbonitrile (5g).** To a stirred solution of *tert*-butoxide (60 mg, 0.5 mmol) in NMP (2 mL) was added under argon a mixture of cyclohexanecarbonitrile (**1c**; 160 mg, 1.5 mmol) and styrene (210 mg, 2 mmol). The reaction was stirred for 15 h at rt. Water (3 mL) and CH_2Cl_2 (25 mL) were added, and the resulting solution was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 1:1 CH_2Cl_2/pentane) to give the desired product **5g** (290 mg, 91% yield). **Method B: preparation of 2-(2-phenylethyl)-3,4-dihydro-1(2*H*)-naphthalenone (6c).** The reaction was carried out as above using DMSO instead of NMP as solvent. To a stirred solution of potassium *tert*-butoxide (90 mg, 0.8 mmol) in DMSO (2.5 mL) were added α-tetralone (**3a**; 600 mg, 6 mmol) and styrene (210 mg, 2 mmol). The reaction mixture was vigorously stirred for 15 h at 40 °C. After the same workup procedure as described above, the crude product was purified by flash chromatography (silica gel, CH_2Cl_2) to give the desired product **6c** (340 mg, 68% yield).