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An efficient conjugate hydrocyanation of chalcones and related enones with TMSCN under solvent- and additive-free microwave conditions

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Abstract—A first example of solvent- and additive-free 1,4-addition reaction of α,β-unsaturated ketones such as chalcones, 3-nonen-2-one and benzalacetone with trimethylsilyl cyanide (TMSCN) is described. The addition of TMSCN to chalcones, 3-nonen-2-one, and benzalacetone under microwave irradiation in the absence of Lewis or Brønsted acids and solvents, yielded the corresponding β-cyanoketones in good to moderate yields, as quite rapidly as in 5 min. No systematic substituent effect of chalcones on the yields was observed. No reaction of α,β-unsaturated esters such as methyl cinnamate with TMSCN took place under the same conditions.

Conjugate hydrocyanation of α,β-unsaturated carbonyl compounds is useful reactions in organic chemistry, because the resulting β-cyanoadducts can be converted to γ-aminobutyric acids (GABA analogues and derivatives) under reducing conditions. One of the most powerful and ubiquitous methods for introduction of a cyano group would be the reactions of ketones with TMSCN. Specifically, the reaction of *p*-benzoquinones with TMSCN afforded only 1,2-adducts which serve as a carbonyl protection.[1] It is reported that the reactions of enones with TMSCN in the presence of base catalysts gave almost selectively 1,2-adducts.[2–4] In contrast, employing Lewis acid catalysts such as Et_2AlCN,[5] Et_3Al,[6] $AlCl_3$,[7] and $SnCl_2$,[7] the selective 1,4-additions took place. Recently, two excellent methods of catalytic enantioselective conjugate addition of cyanide using TMSCN were reported by Jacobsen and co-workers[8] and Shibasaki and co-workers.[9] As far as we searched, acid additives were essential for selective 1,4-addition reactions of enones with TMSCN.

We have been interested in the organic reactions under non-conventional conditions such as high pressure and microwave irradiation. These reaction conditions accelerate reaction rates and sometimes yield unexpected products.[10] We have reported the enantioselective trimethylsilylcyanation of acetophenone catalyzed by Ti-triol under high pressure.[11] In continuation of our studies using non-conventional methods, it occurred to us that microwave irradiation might assist such 1,2- and/or conjugate additions using TMSCN without additive and solvent. This was indeed the case.[12] Quite interestingly, under microwave conditions, a variety of chalcones underwent rapidly and regioselectively conjugate additions with TMSCN without additive and solvent. This is a subject of the present Letter.

Representatively, the reaction of (*E*)-chalcone (1 equiv) and TMSCN (2 equiv) without solvent and any additive, proceeded smoothly by the irradiation of microwave and completed within 5 min. The crude mixture was subjected to evaporation in vacuo to remove TMSCN, and the resulting mixture in THF was treated by TBAF for 5 min to give a single product after column chromatography on SiO_2. An inspection of ^1H and ^{13}C NMR established that the product was not the 1,2-adduct but 1,4-adduct **1**, no 1,2-adduct being observed in the present case (Scheme 1).[13]

Further successful examples of the reactions of (*E*)-chalcones with TMSCN under the same conditions[13] are illustrated in Table 1. Curious substituent effects on the yields should be noted. Thus, the chalcones with such groups as H, CH_3, OCH_3, and F either at 4 or 4′, the 1,4-adducts were obtained in good to moderate

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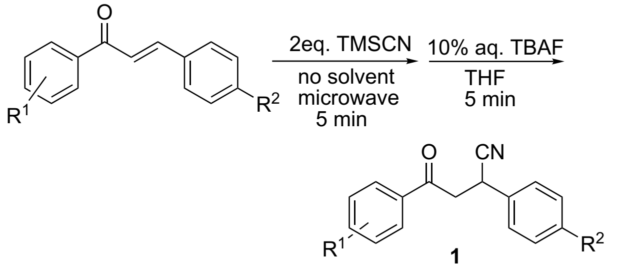

Scheme 1. Microwave assisted reactions of chalcones with TMSCN.

Table 1. β-Cyanoketones **1** from chalcones and TMSCN

Entry	R^1	R^2	Yield[a,b] (%)	mp[c] (°C)
1	H	H	87	122.5–125 (lit. 126–127 (EtOH))[14]
2	*p*-CH_3	H	69 (13)	71–73
3	H	CH_3	68 (13)	135–137 (lit. 135–136 (EtOH))[14]
4	*p*-OCH_3	H	72 (10)	Oil
5	H	OCH_3	65 (11)	113–114
6	*p*-F	H	75 (12)	132–135
7	H	F	71 (10)	97–100.5
8	*p*-Cl	H	72 (20)	116–118 (lit. 122)[15]
9	H	Cl	27 (33)	112–113 (lit. 115–117 (EtOH))[14]
10	*p*-Br	H	27 (36)	122–124 (lit. 124)[15]
11	*m*-Br	H	62 (15)	86–87
12	H	Br	13 (59)	122–123

[a] Isolated yields and not optimized.

[b] Recovered starting material was shown in the parenthesis.

[c] Analytically pure samples were obtained by recrystallization from ethanol.

yields (Table 1, entries 1–7), whereas the chalcones possessing a halogen group such as Cl and Br either at 4 or 4′ position, the 1,4-adducts were obtained only in low yields (Table 1, entries 8–10, 12). However, the chalcone having Br at 3 position gave the adduct in a pretty good yield (entry 11). In any event, no 1,2-adduct was obtained in our hands and the starting materials were recovered.

In order to help clarify the scope and limitation of the present method, some reactions of the enones other than chalcones were performed under the same conditions. For instances, 3-nonen-2-one with TMSCN afforded the 1,4-adduct in a 65% yield along with 24% recovery of 3-nonen-2-one, and benzalacetone with TMSCN gave the 1,4-adduct albeit in a 20% yield with 38% recovery of benzalacetone. Unfortunately, however, α,β-unsaturated esters such as methyl cinnamate did not undergo 1,4-addition at all, the starting material being recovered (Scheme 2).

In conclusions, we disclosed a highly efficient 1,4-addition reactions of chalcones and the related enones with TMSCN under microwave irradiation. Without additive and solvent, the reactions proceed rapidly and regioselectively to give the corresponding 1,4-adducts generally in good to moderate yields. Further investigations employing other kinds of enones such as α,β-unsaturated steroid hormones are under way and will be reported in due course.

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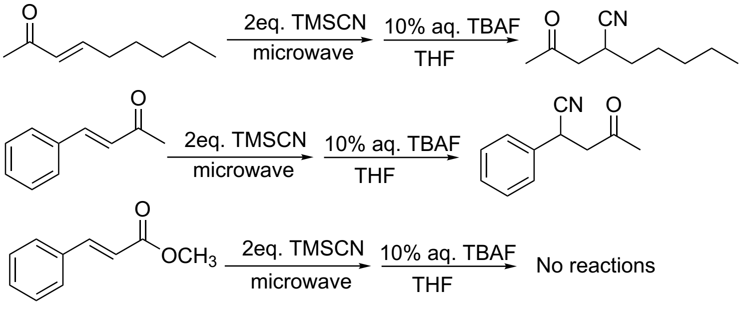

Scheme 2. Microwave assisted reactions of some enones other than chalcones.

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13. *Representative experimental procedure*: A mixture of (*E*)-chalcone (1 mmol) and TMSCN (2 mmol) were irradiated (CEM Discover, 200 °C) for 5 min. After cooling to rt, the mixture was evaporated in vacuo and dissolved in THF (5 mL) to which 10% aqueous solution of TBAF (0.5 mL) was added at rt, and then the solution was stirred for 5 min at rt. Water (5 mL) was added to the solution, and the organic layer was extracted with ethyl acetate (10 mL). The organic layer was washed by brine (10 mL), and dried over $MgSO_4$. Ethyl acetate was evaporated and the resulting oil was subjected to a short column chromatography on SiO_2 using ethyl acetate and hexane (1:1) as the eluent to afford 1,4-adduct. All isolated products gave satisfactory elemental and spectral data (^{1}H NMR, ^{13}C NMR, Anal) and were in agreement with those reported in the literature.[14] The selected spectral data of the 1,4-adduct: Compound **1** ($R^1 = H$, $R^2 = H$): colorless needles, mp 122.0–125.0 (EtOH), ^{1}H NMR ($CDCl_3$) δ: 3.51 (1H, dd, $J = 6.0$, 17.9 Hz), 3.73 (1H, dd, $J = 7.9$, 17.9 Hz), 4.58 (1H, dd, $J = 6.0$, 7.9 Hz), 7.31–7.54 (8H, m), 7.57–7.64 (1H, m), 7.92–7.96 (1H, m); ^{13}C NMR ($CDCl_3$) δ: 31.9, 44.5, 120.6, 127.5, 128.1, 128.4, 128.8, 129.3, 133.9, 135.3, 135.7, 194.7, Anal. Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.27; H, 5.38; N, 5.95.
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