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KHMDS Enhanced SmI_2-Mediated Reformatsky Type α-Cyanation

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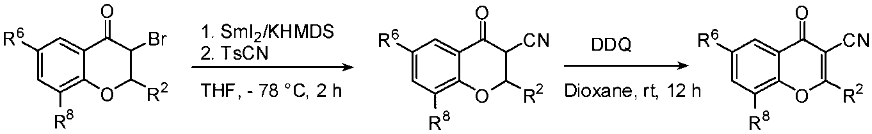
ABSTRACT



A novel combination of SmI_2, KHMDS, and TsCN can be utilized to introduce a cyano group into structurally diverse and highly sensitive 2-alkyl-chroman-4-ones. Subsequent oxidation allows the formed 2-alkyl-3-cyanochromones to be isolated in yields ranging from 49 to 77%. In addition, α-bromoketones and esters were found to undergo equally effective α-cyanation.

Carbon−carbon bond-forming reactions are central to chemical synthesis, and their development is of paramount importance. The Reformatsky reaction, originally defined as a zinc-promoted addition of α-halo esters to carbonyl compounds, represents an important member of this family of reactions.[1] A major breakthrough in the Reformatsky reaction came with the replacement of zinc with the mild reducing agent SmI_2 as a metal equivalent.[2] The use of divalent samarium-based reagents has seen a dramatic increase during the last several decades both in functional group reductions and various coupling reactions.[3] The reactivity of SmI_2 can be adjusted with the addition of additives or solvents,[4] but to the best of our knowledge there is no study on the effect of various additives on the SmI_2-mediated Reformatsky reaction. For some years we have been interested in the synthesis of 2,3,6,8-tetrasubstituted chromone derivatives and in exploring their properties, e.g., as scaffolds for peptidomimetics.[5] As a part of this study, we wished to install a cyano group in the 3-position of 2-alkyl-3-bromo-chroman-4-ones. Cyanation in an α-position to a carbonyl may seem like a trivial transformation, but few reliable methods exist.[6] Examples of successful strategies include formation of the enolate and reaction with various electrophilic cyanide equivalents like tosyl cyanide.[7] Unfortunately, all attempts to introduce the nitrile using standard conditions failed due to the high sensitivity of the chroman-4-ones.[8] Instead, a SmI_2-mediated Reformatsky-type reaction

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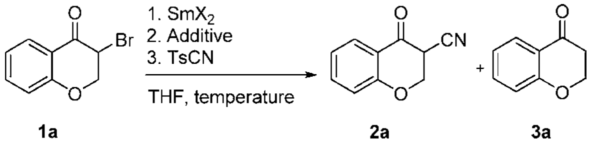
was somewhat promising as we obtained the desired product in low to moderate yields. Herein we report the effects of various additives and the use of $SmBr_2$[9] and $Sm(HMDS)_2$[10] on the Reformatsky reaction.

Initial experiments with 3-bromo-chroman-4-one **1a** as a model substrate using SmI_2 (2.2 equiv) and tosyl cyanide (1.0 equiv) at room temperature resulted in an undesired reduction to yield **3a** (entry 1, Table 1). HMPA is known to facilitate various SmI_2-mediated coupling reactions, possibly by stabilizing radical intermediates and increasing the reduction potential of SmI_2.[11] However, HMPA is considered highly carcinogenic, and its use is banned in many countries, including Sweden. Hence, a selection of alternative additives such as TMG, TMPA, and TPPA were evaluated (Figure 1). Indeed, addition of the HMPA analogues TPPA and TMPA at room temperature gave increased yields of **2a** (entries 3 and 4), indicating that the use of an additive is crucial for a successful coupling. Considerably better selectivity toward **2a** was obtained when the temperature was lowered to −78 °C and the formation of the expected samarium enolate[12] was allowed to proceed for an hour before the tosyl cyanide was added (entry 5).

Table 1. Screening of Optimal Reaction Conditions[a]



entry	SmX_2	additive (equiv)[b]	t/°C	2:3[c]
1	SmI_2	none	rt	1:99
2	SmI_2	TMG (1)	rt	1:99
3	SmI_2	TPPA (1)	rt	6:94
4	SmI_2	TMPA (1)	rt	12:88
5	SmI_2	none	−78	60:40
6	$Sm(HMDS)_2$	none	−78	13:87
7	$SmBr_2$	none	−78	1:99
8	SmI_2	TPPA (1)	−78	79:21
9	SmI_2	TPPA (2.5)	−78	68:32
10	SmI_2	TPPA (5.0)	−78	68:32
11	SmI_2	TMG (0.4)	−78	89:11
12	SmI_2	KHMDS (1)	−78	97:3
13[d]	SmI_2	KHMDS (1)	−78	99:1

[a] The reaction was evaluated using GC/MS after complete workup. The product yield was determined comparing peak area to an internal standard using authentic samples as reference. [b] Equivalents of additive to Sm(II). [c] Complete conversion of starting material was noted for all entries. [d] 2.0 equiv of TsCN was used.

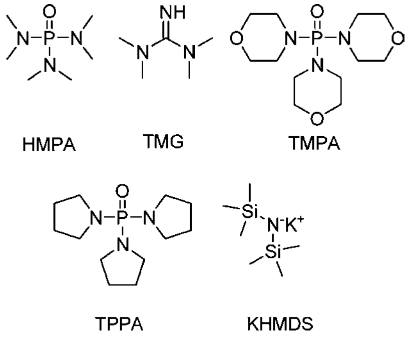


Figure 1. Structures of the additives used for screening of reaction conditions.

In an effort to improve the conversion of **1a** into **2a** we prepared a solution of $Sm(HMDS)_2$ by adding the potassium salt of hexamethyldisilazane (KHMDS) to a SmI_2 solution in THF with the instantaneous precipitation of potassium iodide. This reagent was found to give significantly lower selectivity toward **2a** than SmI_2 alone (entry 6). Upon replacing SmI_2 with $SmBr_2$, no product could be detected (entry 7), which led us to abandon both these reagents.

The conversion of **1a** into **2a** was significantly enhanced upon addition of 1 equiv of TPPA to the SmI_2 solution at −78 °C, but beyond this amount the conversion to **2a** was again lowered probably due to an increase in the reduction potential of SmI_2 (entries 8−10). This gave us the idea to use a substoichiometric amount of additive, and to our delight a further increase in the selectivity toward **2a** was noted when using 0.4 equiv of TMG as additive (entry 11).

Amazingly, when this strategy was utilized for the addition of KHMDS to SmI_2, a close to quantitative conversion of **1a** into **2a** (entry 12) was achieved. The product ratio was improved slightly with an additional equiv of tosyl cyanide (entry 13). This almost complete reversal in outcome of the reaction indicates that we have discovered a combination with unique reactivity.[13] However, a heteroleptic Sm(II) complex with iodide and HMDS has been described, but it has not been detected in solution due to very fast equilibrium favouring homoleptic species.[14] The reason for the observed reactivity is unclear at present, but possibly the heteroleptic

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(8) Attempts to introduce a nitrile using 3-bromo-chroman-4-one and sodium cyanide as the nucleophile were unsuccessful, and so was the method of Kahne et al. (ref 7) using either LDA or LHMDS to deprotonate 2,6,8-trisubstituted chroman-4-ones followed by addition of tosyl cyanide as electrophile.

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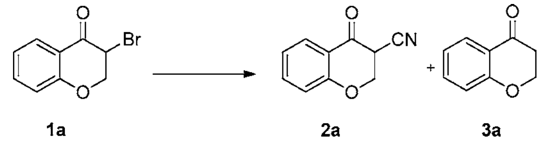


	2a	3a
SmI_2	60%	40%
"SmI(HMDS)"	99%	1%
$Sm(HMDS)_2$	13%	87%

Figure 2. Addition of 1 versus 2 equiv of KHMDS dramatically influences the outcome of the reaction.

species is very reactive, compensating for its low concentration. Alternatively there is a cooperative effect involving $Sm(HMDS)_2$ and SmI_2 (Figure 2).

Inspired by this exceptional result, we did not hesitate to evaluate other electrophiles. Surprisingly, when using cyanogen bromide as an electrophile, only reduction occurred to yield **3a** with both TPPA and KHMDS additives. Reactions with acetyl chloride, benzaldehyde, and 2-nitropropene all gave the expected product but only in very low yields.[15] Benzyl bromide, butyl chloride, phenyl isocyanate, di-*tert*-butyl azodicarboxylate, *N*-methylene benzylamine, DMF, or chloromethylenemorpholinium chloride[16] gave no detectable product according to GC/MS and ^{1}H NMR spectroscopy. We can therefore conclude that tosyl cyanide so far is the electrophile most suitable for this intermolecular Reformatsky reaction.

Using the optimized conditions from Table 1, the 3-cyanochroman-4-one **2a** was obtained in high yields according to both GC/MS and ^{1}H NMR spectroscopic analysis of the crude product. However, **2a** proved to be extremely unstable and decomposed when exposed to all forms of chromatographic purification techniques.[17] To circumvent this particular problem, the crude product was oxidized with DDQ in dioxane[18] directly as the corresponding chromone derivative was more stable.

The obvious option to use 3-bromo-chromones directly in the Reformatsky reaction was however not successful, and no product could be isolated.

The reaction was further investigated using a structurally diverse set of 3-bromo-chroman-4-ones (**1a**−**g**)[19] and 3-bromoflavanones (**1h** and **1i**). Previously we have shown that the 3-position in 2-alkyl chromones can be substituted with an amine, hydroxyl, or bromine group, but attempts to introduce a nitrile group in the 3-position have so far been unsuccessful as described above.[20] The optimized reaction conditions from Table 1 followed by DDQ oxidation resulted in the formation of 3-cyanochromones in fair to excellent yields (42−77% over two steps, Table 2).

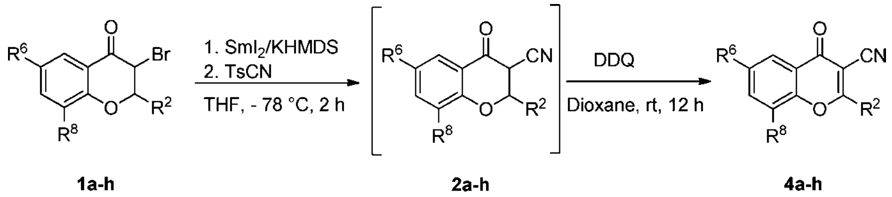
The reaction shows a robust behavior as neither electron-donating nor electron-withdrawing substitution seems to influence the isolated yield. Substitution in the 2-position with alkyl groups (entries 4−7, Table 2) gave fair to good yields over two steps (42−76%).

It is also worth noting that both the aromatic halogens[21] in **1c**, **1e**, **1f**, and **1i** as well as the methyl ester in substrate **1g** (Table 2) survived this treatment. These findings suggest that the reaction is suitable for substrates containing sensitive functional groups.

It was also evaluated if the method was applicable to the formation of flavone derivatives[22] (entries 8 and 9, Table 2), and it was found that the yields again were good for both substrates with and without ring substituents, proving the robustness of the method.

From the optimization study (Table 1), we could conclude that the yield of the chroman-4-one **2a** was close to quantitative; however, this is not reflected in the isolated yield of this particular product. Therefore, the conversion of

Table 2. Synthesis of 2-Alkyl-3-cyano-chromones from 2-Alkyl-3-bromo-4-chroman-4-one Derivatives



entry	substrate	R^2	R^6	R^8	cis:trans **1**	cis:trans **2**	product	yield (%)[a]
1	**1a**	H	H	H	n/a	n/a	**4a**	49
2	**1b**	H	Me	H	n/a	n/a	**4b**	77
3	**1c**	H	Cl	H	n/a	n/a	**4c**	62
4	**1d**	n-C_5H_{11}	OMe	H	75:25	45:55	**4d**	42
5	**1e**	Cy-C_6H_{11}	Cl	Br	99:1	25:75	**4e**	76
6	**1f**	$PhCH_2CH_2$	Cl	Br	80:20	45:55	**4f**	59
7	**1g**	n-C_5H_{11}	CH_2COOMe	Br	77:23	32:68	**4g**	61
8	**1h**	Ph	H	H	65:35	25:75	**4h**	65
9	**1i**	Ph	Cl	Br	75:25	40:60	**4i**	61

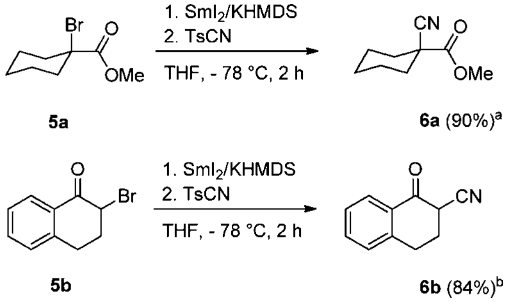
[a] Isolated yield over two steps.

chroman-4-one **2a** into chromone **4a** was examined with gas chromatography, and from this it was evident that the concentration of the product was lower after the oxidation step.

Closer inspection of the isolated yields in Table 2 reveals that the results for the 2-alkyl-substituted substrates are consistently better. This can be due to an increased stability of the resulting 2-substituted cyanochroman-4-one intermediate, and indeed, some were stable enough for chromatographic purification. This shows that this reaction is a feasible route for the preparation of 2-alkyl-3-cyanochroman-4-ones.[23] During the course of this work, we needed gram quantities of 3-cyanochromone **4f**, and gratifyingly it was found that the reaction gave an equal yield on a larger scale.

α-Bromo esters and ketones were evaluated under the same reaction conditions (Scheme 1). Cyclic α-bromo ester **5a** gave an excellent yield of cyano ester **6a**. The cyclic ketone **5b** was also efficiently cyanated to form **6b**, but the method was unfortunately not successful for acyclic α-bromo methyl ketones. Kahne et al.[7] obtained similar results that the resulting products are highly sensitive toward polymerization, thus explaining the low yields.[24] This is also supported by the fact that chromatographic analysis displayed no starting material or dehalogenated product.

Scheme 1. α-Cyanation of α-Halo Carbonyl Compounds



[a] Isolated yield. GC/MS yield determined to 93% comparing to an internal standard. [b] Yield determined from GC/MS analysis comparing to an internal standard.

In conclusion, a novel and efficient synthetic method for α-cyanation of ketones and esters using a SmI$_2$/KHMDS-mediated Reformatsky reaction has been developed. The results presented herein indicate that this novel reagent exhibits a unique reactivity in the reaction considered herein. Furthermore, the method is applicable to 3-bromo-chroman-4-ones with a variety of substituents. Various HMPA-like additives were evaluated and gave good results which indicates that these also may serve as efficient additives for SmI$_2$-mediated reactions.

We are presently studying the mechanistic details of this reaction to develop conditions allowing an even broader scope.

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Supporting Information Available: Contains detailed experimental procedures and complete characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) The yields were estimated to be approximately 10−20% with GC/MS analysis compared with an internal standard.

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