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Tandem Carbon–Carbon Bond Constructions via Catalyzed Cyanation/Brook Rearrangement/C-Acylation Reactions of Acylsilanes

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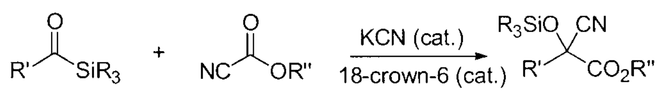
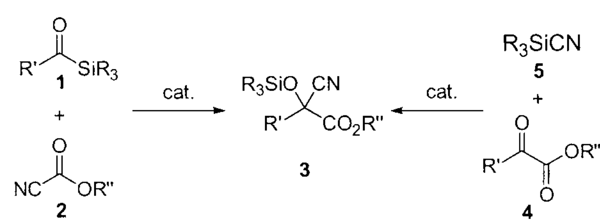
ABSTRACT



A tandem nucleophile-catalyzed cyanation/Brook rearrangement/C-acylation has been developed. Phase transfer cocatalysts facilitate cyanide-catalyzed reactions between acylsilanes and cyanoformates to afford protected tertiary carbinol products. A catalytic cycle is proposed involving cyanation of an acylsilane, [1,2]-Brook rearrangement, and C-acylation of the derived carbanion by a cyanoformate ester. The reaction offers an efficient method for the preparation of functionalized, unsymmetrical malonic acid derivatives.

Tandem or domino reactions can provide efficient pathways for the rapid introduction of molecular complexity.[1] The principal challenge associated with the design of new domino reactions is the strategic placement of functionality in the starting materials that will enable subsequent steps in the reaction sequence. Acylsilanes have been noted as particularly useful functional groups in this context.[2] Nucleophilic addition to acylsilanes frequently triggers carbon-to-oxygen migration of the silyl group (Brook rearrangement),[3] the product of which is a carbanion that can participate in additional bond constructions. This Letter describes a new nucleophile-catalyzed cyanation/Brook rearrangement/C-acylation reaction between cyanoformate esters and acylsilanes (Scheme 1). The products of these domino reactions are unsymmetrical malonic acid derivatives (**3**) that result from the formation of two new carbon–carbon bonds and a protected tertiary carbinol.

Scheme 1



Examples of synthetic approaches to α-cyano α-hydroxy esters and their derivatives have been reported; all involve the formation of a single carbon–carbon bond as the key step. Lewis acid- or Lewis base-promoted additions of silyl cyanide reagents (**5**) to α-keto esters (**4**) deliver silyloxy cyanoesters (**3**).[4,5] An ene reaction between 1-hexene and ethoxalyl cyanide forms a different C–C bond and yields the unprotected carbinol.[6] Alternatively, such cyano carbonyl

(1) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136.
(2) Moser, W. H. *Tetrahedron* **2001**, *57*, 2065–2084.
(3) Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77–84.
(4) Foley, L. H. *Synth. Commun.* **1984**, *14*, 1291–1297.
(5) Wilkinson, H. S.; Grover, P. T.; Vandenbossche, C. P.; Bakale, R. P.; Bhongle, N. N.; Wald, S. A.; Senanayake, C. H. *Org. Lett.* **2001**, *3*, 553–556.
(6) Achmatowicz, O., Jr.; Szymoniak, J. *Tetrahedron* **1982**, *38*, 1299–1302.

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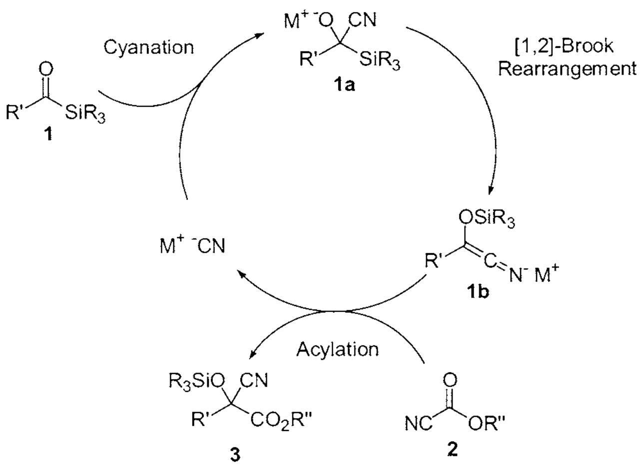
compounds may be prepared via C-acylation of carbanions derived from suitably protected cyanohydrins.[7,8] An asymmetric variant of this reaction involving an auxiliary controlled C-acylation of a chiral cyanohydrin phosphate with benzoyl chloride was recently disclosed by Schrader.[9] Takeda, Reich, and Degl'Innocenti have reported generation of carbanionic cyanohydrin derivatives via reactions of acylsilanes (**1**) with various $^{-}$CN sources.[10-12] The nucleophiles derived from [1,2]-Brook rearrangement were trapped in protonation and alkylation reactions, but the analogous acylation reactions have not been reported to the best of our knowledge.

The latter publications led us to consider the possibility of employing cyanoformates[13,14] as acylating agents for the silyl cyanohydrin carbanions. The proposed catalytic cycle that resulted from this idea is pictured in Scheme 2.

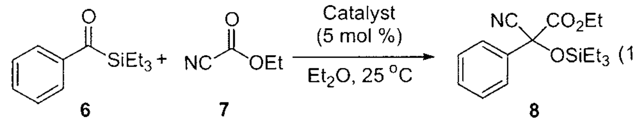
Scheme 2



Nucleophilic addition of a metal cyanide to an acylsilane (**1**) would generate a tetrahedral intermediate **1a** poised to undergo [1,2]-Brook rearrangement. Following migration of silicon from carbon to oxygen, C-acylation of the resulting nitrile enolate **1b** with a cyanoformate ester (**2**) would give the desired product and regenerate the metal cyanide, completing the catalytic cycle.

To assess the viability of the proposed reaction scheme (Scheme 2), a number of catalysts and cocatalysts were evaluated (Table 1). In the presence of catalytic quantities of KCN, phenyl triethylsilyl ketone (**6**) reacted slowly with

Table 1. Catalyst Evaluation for Cyanation/Brook Rearrangement/C-Acylation Reactions of Acylsilanes (Eq 1)[a]



entry	catalyst	time (h)	yield (%)[b]
1	KCN	36	29[c]
2	KCN/18-crown-6	4–5	86
3	KCN/Bu_4NBr	15	83
4	KCN/Bu_4PBr	15	74
5	quinuclidine	36	69[d]
6	none	36	0

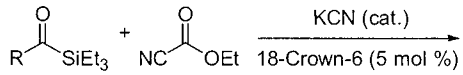
[a] $PhC(O)SiEt_3$ (1.0 equiv), $NCCO_2Et$ (1.1 equiv). [b] Isolated yield of analytically pure material. [c] Percent conversion based on ^{1}H NMR spectroscopy of the unpurified reaction mixture. [d] Catalyst concentration = 20 mol %, C_7H_8, 25 °C.

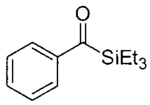
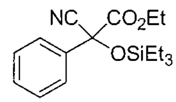
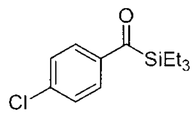
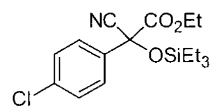
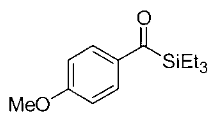
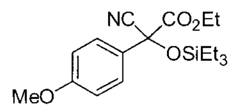
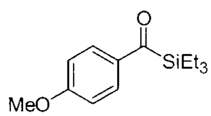
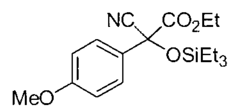
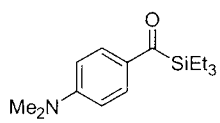
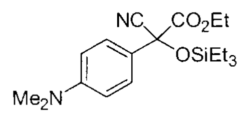
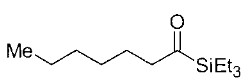
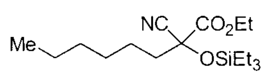
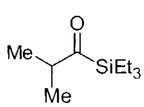
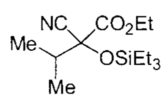
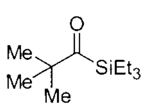
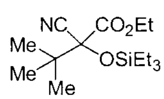
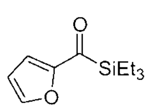
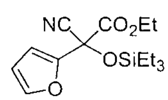
ethyl cyanoformate in Et_2O to afford the desired acylation product **8** in low yield (entry 1). Speculating that the limited solubility of the KCN in the medium was hindering reactivity, phase transfer catalysts were employed to increase the concentration of $^{-}$CN in solution. The commonly used KCN cocatalyst, 18-crown-6,[15] proved to be optimal for the Brook rearrangement sequence and could be employed at relatively low catalyst loadings (5 mol %, entry 2). The reaction also proceeded with cocatalysis by tetrabutylammonium or tetrabutylphosphonium bromide, albeit at a slower rate (entries 3 and 4). The tertiary amine quinuclidine (entry 5) could also be utilized as a catalyst in the absence of KCN, although slower reaction times were observed relative to the KCN/18-crown-6 system. The success of this experiment suggests that a different mechanism, one analogous to O-acylation reactions conducted by Deng, may be operative for this catalyst.[16] A control experiment demonstrated that **6** and **7** do not react in the absence of a catalyst (entry 6).

With the identification of 18-crown-6 and KCN as an efficient catalyst system, the reaction scope was studied using a variety of acylsilanes.[17] Collectively, aryl acylsilanes gave moderate to excellent yields (66–97%, Table 2, entries 1–5 and 9). The electron-poor aryl acylsilanes reacted faster (1–2 h) than their electron-rich counterparts (4–24 h), which required more forcing conditions (toluene, 110 °C). Alkyl acylsilanes gave moderate to good yields (49–73%, entries 6–8) with reaction times closer to that of the electron-deficient aryl acylsilanes (1.5–4 h). Optimum yields for enolization-prone alkyl acylsilanes were realized through slow acylsilane addition to a solution of cyanoformate and

(7) Babler, J. H.; Marcuccilli, C. J.; Oblong, J. E. *Synth. Commun.* **1990**, *20*, 1831–1836.
(8) Hünig, S.; Wehner, G. *Chem. Ber.* **1980**, *113*, 302–323.
(9) Schrader, T. *Chem. Eur. J.* **1997**, *3*, 1273–1282.
(10) Takeda, K.; Ohnishi, Y. *Tetrahedron Lett.* **2000**, *41*, 4169–4172.
(11) Reich, H. J.; Holtan, R. C.; Bolm, C. *J. Am. Chem. Soc.* **1990**, *112*, 5609–5617.
(12) Degl'Innocenti, A.; Ricci, A.; Mordini, A.; Reginato, G.; Colotta, V. *Gazz. Chim. Ital.* **1987**, *117*, 645–648.
(13) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425–5428.
(14) Crabtree, S. R.; Mander, L. N.; Sethi, S. P. *Org. Synth.* **1991**, *70*, 256–264.
(15) Evans, D. A.; Truesdale, L. K. *Tetrahedron Lett.* **1973**, 4929–4932.
(16) Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 6195–6196.
(17) Acysilanes were prepared in three steps from the corresponding aldehydes. See Supporting Information for details. For reviews on the synthesis and chemistry of acylsilanes, see: (a) Cirillo, P. F.; Panek, J. S. *Org. Prep. Proc. Int.* **1992**, *24*, 553–582. (b) Page, P. C. B.; Klair, S. S.; Rosenthal, S. *Chem. Soc. Rev.* **1990**, *19*, 147–195. (c) Reference 2.

Table 2. Catalytic Cyanation/Brook Rearrangement/C-Acylation of Acylsilanes (Eq 2)[a]



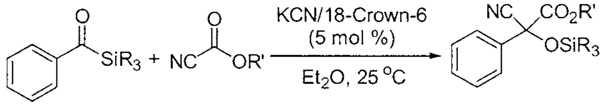
entry	acylsilane	product	solvent	temp (°C)	time (h)	yield[b] (%)
1			Et_2O	25	2	81
2			Et_2O	25	1	74
3			Et_2O	25	12	62[c]
4			C_7H_8	110	3	85[d]
5			C_7H_8	110	24	97
6			Et_2O	25	1.5	73[e]
7			Et_2O	25	1.5	61[e]
8			Et_2O	25	3-4	49[e]
9			C_7H_8	110	4-5	66

[a] $RC(O)SiEt_3$ (1.0 equiv), $NCCO_2Et$ (1.1 equiv) unless otherwise stated. [b] Isolated yield of analytically pure material; average of at least two experiments. [c] Percent conversion based on ^1H NMR spectroscopy; 50 mol % 18-crown-6, 5.0 equiv of $NCCO_2Et$. [d] 18-Crown-6 concentration = 20 mol %. [e] 18-Crown-6 (60 mol %) and $NCCO_2Et$ (4 equiv); slow addition of acylsilane.

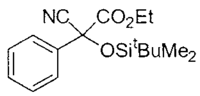
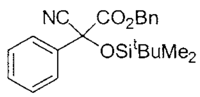
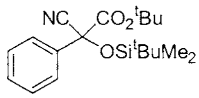
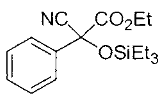
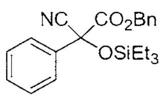
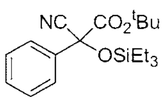
catalyst. This procedure minimized the competing proton-transfer pathway, and the cyanohydrin byproduct (10%-33%) arising from protonation of **1b** was separable from the desired product by chromatography. The alkyl acylsilanes (entries 6−8) were qualitatively as reactive as their aryl counterparts. To a first approximation, yields correlated with the steric demand of the substrate. It has not yet been ascertained if the rate-limiting step is the same for all substrates. The reactivity profile observed for the aryl acylsilanes could reasonably implicate either the cyanation or Brook rearrangement steps as rate-limiting.

The substrate scope was further investigated in the context of silane and cyanoformate structures (Table 3). Yields were good to excellent (72−92%) when either the silyl group or the cyanoformate was varied. In general, it appears that the more robust *tert*-butyl dimethylsilyl acylsilane afforded higher yields than the triethylsilyl acylsilane. In these reactions, the carbinol protecting group is selected through

Table 3. Variation of Silane and Ester Substituents in Catalyzed Cyanation/Brook Rearrangement/C-Acylation Reactions (Eq 3)[a]



(3)

entry	acylsilane	(R')	product	time (h)	yield (%)[b]
1	$SiMe_2{}^tBu$	Et		2	92
2	$SiMe_2{}^tBu$	Bn		2	87
3	$SiMe_2{}^tBu$	^{t}Bu		1	87
4	$SiEt_3$	Et		2	81
5	$SiEt_3$	Bn		2	80
6	$SiEt_3$	^{t}Bu		12	72

[a] $PhC(O)SiR_3$ (1.0 equiv), $NCCO_2R'$ (1.1 equiv). [b] Isolated yield of analytically pure material; average of at least two experiments.

the choice of the acylsilane. The fact that there is little qualitative difference in reactivity for the $-SiEt_3$ or $-Si^t$-$BuMe_2$ groups suggests good flexibility with respect to this and future chemistry. One exception is phenyl trimethylsilyl ketone ($PhC(O)SiMe_3$), which was successfully employed in these reactions but with formation of variable quantities of the derived ketoester ($PhC(O)CO_2Et$) as a result of TMSCN elimination.

A new catalyzed cyanation/Brook rearrangement/C-acylation sequence has been developed that results in the efficient construction of functionalized unsymmetrical malonic acid derivatives from readily accessible starting materials. The operationally simple reaction proceeds at ambient temperature or greater and conveniently introduces silyl group protection of the resulting tertiary carbinol with concomitant formation of two new carbon−carbon bonds. Reasonable generality of the reaction with a range of acylsilanes and cyanoformates has been demonstrated. The development of an asymmetric variant is a current focus of our research and will be reported in due course.

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

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