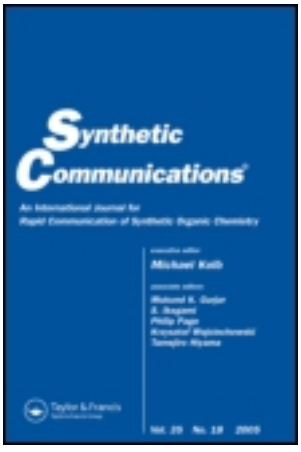

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Silica Gel-Supported bis(Trimethylsilyl) Chromate: Oxidation of 1,4-Dihydropyridines to Pyridines

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Silica Gel–Supported bis(Trimethylsilyl) Chromate: Oxidation of 1,4-Dihydropyridines to Pyridines

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Abstract: An efficient and convenient method for the oxidation of 1,4-dihydropyridines mediated by silica gel–supported bis(trimethylsilyl) chromate in refluxing CH_2Cl_2 is reported.

Keywords: Oxidation, DHP, Hantzsch, Bistrimethylsilyl chromate, Supported silica gel

Several 1,4-dihydropyridines (DHPs) are important cardiovascular drugs because of their calcium antagonistic effect.[1] In the human body, these compounds are oxidized. They serve as effective redox catalysts under mild conditions, modeling the NAD(P)H coenzyme to allow study of its oxidation mechanism in a living system[2,3] in the search for new drugs for heart vascular disease.[4,5] In addition, recent studies have suggested that 1,4-DHP derivatives also provide an antioxidant protective effect that may contribute to their pharmacological activity.[6] This effect is not due to the Ca^{2+} antagonist effect but is related to the reactivity of these compounds toward radical species.[7] The oxidation of the dihydropyridine ring is the main metabolic route for these compounds.

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The oxidation of 1,4-DHPs is an important problem in organic chemistry, and several groups have reported oxidation methods including chemical oxidation with ferric or cupperic nitrate on a solid support,[8] ceric ammonium nitrate,[9] ultrasound-promoted oxidation by clay-supported cupric nitrate,[10] oxidation with PPC,[11] nitric acid,[12] aromatization with Magtrone TM,[13] oxidation with manganese triacetate,[14] catalytic oxidation by $RuCl_3$ under oxygen atmosphere,[15] bismuth nitrate pentahydrate,[16] pyridinum dichromate,[17] nitric oxide,[18] urea nitrate, and peroxydisulfide-cobalt(II).[19] More recently the detailed mechanism for the oxidation of 1,4-DHP derivatives has attracted more attention from chemists.[20] However, oxidation with most of these reagents leads to dealkylation at the 4-position or formation of side products.

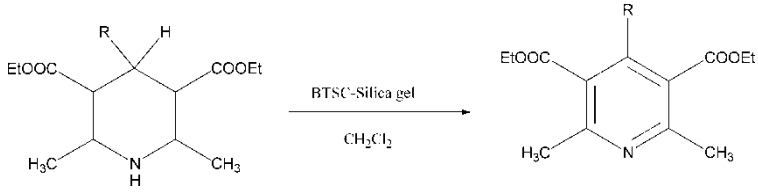
We have recently used bis(trimethylsilyl) chromate as a versatile oxidizing agent;[21] herein we report experimentation for the oxidation of Hantzsch 1,4-dihydropyridines to the corresponding pyridines using bis(trimethylsilyl) chromate in refluxing CH_2Cl_2. In the preliminary examination we found that reaction is very slow, the yield is low, and the isolation of products from the ensuing residues is difficult.

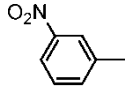
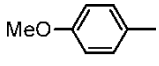
The use of a supported regent[22] has attracted interest because of improved selectivity, reactivity, and associated ease of manipulation.

In view of ongoing research using solid supports in our laboratory,[23] we used silica gel–supported bis(trimethylsilyl) chromate as an efficient oxidizing agent to effect the 1,4-dihydropyridines to pyridines conversions. We examined various supports such as clay, alumina, and montmorilonite K-10 and found that silica gel provides the best result in terms of formation of pure products. Dichloromethane is the solvent of choice in this conversion for the optimum yield. The general applicability, versatility, and scope of this supported reagent is proved by using a variety of 1,4-DHPs including 1,4-DHPs with H, alkyl, benzyl, and heterocycle at the 4-position (Table 1). The salient feature of this reaction is the stability of the substituents at the 4-position, confirmed by spectroscopic and physical data. Substituents at the 4-position are normally dealkylated during aromatization by some existing methods.[24] The other advantages of this method over the existing methods are milder reaction conditions, excellent yields, availability of reagent, and easy workup procedure. The procedure involves simple mixing of 1,4-DHPs, silica gel, and bis(trimethylsilyl) chromate and refluxing them in CH_2Cl_2.

In summary, the present methodology offers an attractive, efficient, and high-yielding method for the aromatization of 1,4-dihydropyridines with keeping the substitutents at 4-position. To show the merit of the present work in comparison with recently reported protocols, we compared the results of the oxidation of entry 3 (Table 1) in the presence of NO, PDC, $Bi(NO_3)_3 \cdot 5H_2O$, $RuCl_2$–O_2, and BTSC–silica gel with respect to reaction times, yields, and the obtained products (Table 2).

Table 1. Oxidation of 1,4-DHPs using BTSC–silica gel



Entry	R	Time (min)	Yield (%)[b]	Observed mp (°C)[a]	Reported
1	H–	20	100	70	69–70[26]
2	H_3C–	30	100	Liq.	Liq.[5]
3	Et–	30	96	Liq.	Liq.[5]
4		20	97	61	61–62[5]
5		40	100	60–62	61–63[26]
6		120	100	50	50[27]
7		120	95.2	Liq.	38–41[26]

[a]Products exhibited physical properties in accordance with the assigned structures.
[b]Yields refer to the isolated pure products.

EXPERIMENTAL

All the dihydropyridines were prepared according to the literature procedure, using the appropriate aldehydes, ammonia, and ethyl acetoacetate.[25] Silica gel 60 for column chromatography was purchased from Merck. All products

Table 2. Results of the oxidation of entry 3 (Table 1) in the presence of BTSC–silica gel and some of other reagents

Entry	Oxidant	Time (h)	Yield of dehydrogenated product (%)	Ref.
1	NO	4	91	18
2	PDC	1	77	17
3	$Bi(NO_3)_3 \cdot 5H_2O$	5	68	16
4	$RuCl_2$–O_2	60	45	15
5	BTSC–silica gel	0.5	100	—

were known; their physical and spectroscopic data were compared with those of authentic samples and found to be identical.

Preparation of bis(Trimethylsilyl) Chromate, Supported on Silica Gel, BTSC–Silica Gel

CrO_3 (3 g, 0.03 mol) was added to a solution of hexamethyldisiloxane (6.4 mL, 0.03 mol) in dichloromethane (40 mL). The reaction mixture was stirred in a 50°C bath for 5 h. Solid CrO_3 dissolved, and the dark red mixture became homogeneous. Silica gel (13 g) was added to the warm reaction mixture and the resulting mixture was stirred for another 5 h. The solvent and other volatile components were removed under reduced pressure to afford 19.3 g of supported reagent.

Oxidation of Hantzsch 1,4-Dihydropyridines: General Procedure

BTSC–silica gel (1.5 g, 2.2 mmol) was added to a solution of 1,4-dihydropyridine (1 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was refluxed for the indicated time (Table 1). The progress of reaction was monitored by TLC using (98 : 2 dichloromethane–ethylacetate) as eluent. After completion of the reaction, the reaction mixture was filtered on a silica-gel pad. The filtrate was evaporated to dryness to afford the corresponding pyridine.

Data

Selected data for 1: Yield: 100%; mp: 70 (lit.[26] 69–70); IR $\bar{\nu}$ (KBr): 755, 1553, 1600, 1730, 2923, 2965 cm^{-1}; ^1H NMR δ ($CDCl_3$): 1.1 (t, 6H, $2CH_3$); 3.0 (s, 6H, $2CH_3$); 4.2 (q, 4H, $2CH_2$); 8.6 (s, 1H).

Selected data for 2: Yield: 100%, liq. (lit.[5] liq.); IR $\bar{\nu}$ (film): 1064, 1560, 1730, 2930, 2984 cm^{-1}; ^1H NMR δ ($CDCl_3$): 1.1 (t, 6H, $2CH_3$); 2.3 (s, 3H), 2.4 (s, 6H, $2CH_3$); 4.2 (q, 4H, $2CH_2$).

Selected data for 3: Yield: 96%, liq. (lit.[5] liq.); IR $\bar{\nu}$ (film): 1238, 1453, 1569, 1730, 2976 cm^{-1}; ^1H NMR δ ($CDCl_3$): 0.8–1.2 (t, 3H); 1.1 (t, 6H, $2CH_3$); 2.4 (s, 6H, $2CH_3$); 2.8 (q, 2H); 4.2 (q, 4H, $2CH_2$).

Selected data for 4: Yield: 97%, mp: 61 (lit.[5] 61–62); IR $\bar{\nu}$ (KBr): 1107, 1561, 1730, 2976, 3015 cm^{-1}; ^1H NMR δ ($CDCl_3$): 1.1 (t, 6H, $2CH_3$); 2.4 (s, 6H, $2CH_3$); 4.2 (q, 4H, $2CH_2$); 7.3 (s, 5H).

Selected data for 5: Yield: 100%, mp: 61–62, (lit.[26] 61–63); IR $\bar{\nu}$ (KBr): 1535–1538, 1560, 1623, 1730, 2965, 3050 cm^{-1}; ^1H NMR δ ($CDCl_3$): 1.1 (t, 6H, $2CH_3$); 2.4 (s, 6H, $2CH_3$); 4.2 (q, 4H, $2CH_2$); 7.7 (d, 2H); 8.2 (s, 1H); 8.3 (m, 2H).

Selected data for 6: Yield: 100%, mp: 50 (lit.[27] 50); IR $\bar{\nu}$ (KBr): 1115, 1292, 1515, 1615, 1730, 2970 cm^{-1}; ^1H NMR δ ($CDCl_3$): 1.1 (t, 6H, $2CH_3$); 2.4 (s, 6H, $2CH_3$); 3.8 (s, 3H, CH_3); 4.2 (q, 4H, $2CH_2$); 6.7 (d, 2H); 7.2 (d, 2H).

Selected data for 7: Yield: 95.2%, liq. (lit.[26] 38–41); IR $\bar{\nu}$ (KBr): 1046, 1107, 1561, 1575, 1730, 2984, 3075 cm^{-1}; ^1H NMR δ ($CDCl_3$): 1.1 (t, 6H, $2CH_3$); 2.4 (s, 6H, $2CH_3$); 4.2 (q, 4H, $2CH_2$); 6.2–6.5 (c, 2H); 7.4 (c, 1H).

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