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Role of quaternaryammonium permanganates in the synthesis of substituted guanidines—a comparative study

Natarajan Srinivasan† and Krishnamurthy Ramadas*

Centre for Agrochemical Research, SPIC Science Foundation, 110 Mount Road, Chennai 600 032, India

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Abstract—Quaternaryammonium permanganate transforms 1,3-diarylthioureas in the presence of an amine to the respective trisubstituted guanidines in excellent yields.

On account of their immense pharmaceutical and agrochemical activities[1] guanidines dominate our recent research efforts. As substituted guanidine is an established NMDA receptor antagonist[2] with anti-acetylcholinesterase activity, it has a special significance for our synthetic interest. We have already emphasized the usefulness of thiourea as an ideal substrate for the preparation of unsymmetrical guanidines of industrial importance.[3] Desulfurization of thioureas utilizing metal oxides is one of the classical methods.[4] Synthetic schemes using phosgene,[5] cyanamide and cyanogen bromide[2,6] are less attractive due to the toxicity of the reagents employed. Guanidines prepared through the intermediacy of carbodiimides[7] are not interesting due to factors such as a tedious preparation procedure and poor stability of the carbodiimides. Reaction of *S*-methylated thioureas with amines leading to the guanidines seems to be less applicable owing to the formation of obnoxious and toxic mercaptans as side products.[8] Synthesis of guanidines from the sulfonic acid obtained by oxidation of unsubstituted thiourea using H_2O_2 has already been reported,[9] and the above method was based on the synthesis by Maryanoff et al.[10] for the preparation of disubstituted guanidines from monosubstituted thioureas. Surprisingly, diaryl thioureas behave differently with hydrogen peroxide to yield thiadiazolidines instead of the expected sulfonic acid, as reported by Kulkarni et al.[11]

Consequently, we have investigated a different procedure for the oxidation of diaryl thioureas under milder conditions. Potassium permanganate is known to oxidize many sulfur-containing compounds like thiols, sulfoxides and disulfides.[12] Many aliphatic thiols[12] and certain cyclic thioureas[13] have been oxidized to sulfonic acid derivatives. A potassium permanganate/acetic acid system oxidizes 2-alkylthio benzothiazole to the sulfonic acid.[14]

Although $KMnO_4$ in aqueous solution is a commonly used oxidant in preparative organic synthesis,[15] it cannot be used advantageously for organic substrates which are poorly soluble in water. The major disadvantage is due to the thermodynamic instability with respect to water.[16]

$$4MnO_4^- + 2H_2O \rightarrow 4MnO_2 + 3O_2 + 4OH^-$$

Therefore, $KMnO_4$ is usually used in excess and the yields are often low, probably due to over-oxidation of the product.[15] Our efforts in oxidizing 1,3-disubstituted thioureas with alkaline and aqueous $KMnO_4$ along with an amine in presence of a phase-transfer catalyst also failed to give the desired product.

This observation led us to examine the use of quaternaryammonium permanganates in non-aqueous media. Organic permanganates have been widely exploited in synthetic organic chemistry and these include bis-pyridyl silver permanganate,[17] bis(2,2′-bipyridyl)copper-(II) permanganate[18] which are known to oxidize alcohols and oximes to carbonyl compounds, aromatic amines to azo compounds and benzylamine to benzaldehyde. Reich et al. reported *cis*-hydroxylation of olefins by triphenylmethylphosphonium permanganate.[19] Permanganates derived from various quater-

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* Corresponding author. Present address: Vice President (R&D), Chemfab Alkalis Limited, Kalapet, Pondicherry, Union Territory, Pin: 605 014, India. Tel.: 0413-655116; fax: 0413-655125; e-mail: chemfab_alkalis@vsnl.com

† Present address: Department of Chemistry, Faculty of Science and Technology, New University Lisbon, 2825-114 Caparica, Portugal. E-mail: srinivasan@dq.fct.unl.pt

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naryammonium salts play a role in several transformations, such as the oxidation of C–C double bonds.[20] Sargent et al. first isolated tetrabutylammonium permanganate as a stable solid and exploited it for the oxidation of aldehydes to carboxylic acids.[16] Chemoselective oxidation of hydrocarbons to alcohols, ethers to esters and cyclic acetals to hydroxyalkyl carboxylates have been reported using benzyltriethylammonium permanganate.[21] Stereospecific *trans*-dichlorination of olefins was achieved by benzyltriethylammonium permanganate with oxalyl chloride.[22] A series of imines were oxidized to nitrones with permanganates under phase-transfer conditions.[23] Cetyltrimethylammonium permanganate has been found to oxidize benzyl alcohols to the corresponding aldehyde or ketone.[24] The use of quaternaryammonium permanganates for the present transformation has no precedent in the literature.

1. Use of quaternaryammonium permanganate—a comparative study

Quaternaryammonium permanganates were prepared[21] in a pure, dry state for the onward reaction with thioureas in the presence of an amine nucleophile, which rapidly furnished the guanidines in appreciable yields.

There was no progress in the reaction when the thiourea and oxidant were allowed to react whereas a notable change was found in the presence of an amine. This prompted us to study the effect of the reagent in the absence of an amine nucleophile but in the presence of a tertiary amine such as triethylamine. Thin-layer chromatography was used to indicate the exclusive consumption of thiourea and formation of a product which might be the oxidized thiourea (sulfinic or sulfonic acid, Scheme 1).

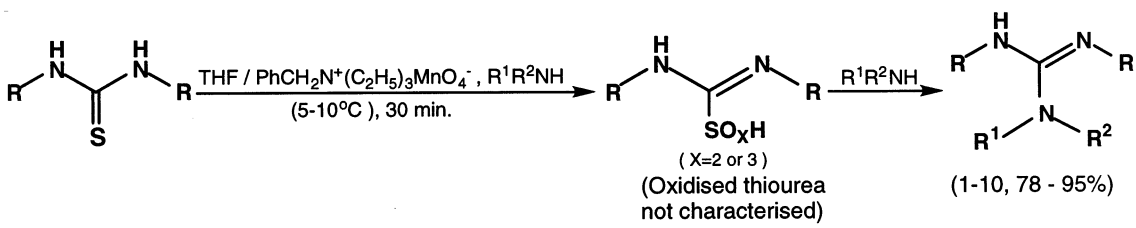
Unfortunately, the product formed rapidly decomposed to a dark brown complex mixture. This is in agreement with an observation in the previous report[25] stating that oxides of thiourea (sulfinic or sulfonic acid) are unstable in basic media. Thus, it is believed that the thiocarbamide reacts with quaternaryammonium permanganate to yield the oxidized thiourea (not characterized), which reacts rapidly with the amine present to form the guanidine (Scheme 1). This is preferred since the sulfonyl group is reported to be displaced about 15 times faster than the corresponding *S*-alkylated species in the case of monosubstituted thioureas.[10] Use of quaternaryammonium permanganate on dialkylthioureas did not bear fruitful results. A comparative study was made using benzyltriethylammonium permanganate (BTEAP), cetyltrimethylammonium permanganate (CTMAP) and tetrabutylammonium permanganate (TBAP) on several thioureas and amines (see Tables 1 and 2).

From the data generated in Table 1, it is clear that benzyltriethylammonium permanganate is better than the other two. CTMAP furnished poor results and the product isolation was rendered difficult due to the formation of a lather during the aqueous work-up. We found that CTMAP is more moisture sensitive and decomposes to a dark brown solid even when storaging for a short time unlike BTEAP or TBAP. Our observations and the results gathered conclude BTEAP to be the reagent of choice. BTEAP can be advantageously used over the other two oxidants since it is stable,[21] shock-resistant and decomposes above 100°C. This makes the reagent convenient to handle unlike copper and silver bis-pyridyl permanganates, which suffer from low stability and are thermally explosive.[17]

In summary, this one-pot synthetic scheme can be exploited for the rapid synthesis of any 1,3-diaryl-2-alkylguanidine in a high yield under mild and simple experimental conditions free from any toxic and obnoxious by-products.

2. Typical procedure for the synthesis of substituted guanidines using benzyltriethylammonium permanganate (BTEAP)

1,3-Diarylthiourea in THF (10 mmol, 20 ml) and amine (20 mmol) were stirred at 5–10°C before the portionwise addition of BTEAP (10 mmol, 3.2 g) over 15 min. The reaction mixture was then stirred for a further 15 min. Work-up involved filtration and washing the residue with THF (2×3 ml). The filtrate, together with the combined washings, was evaporated to leave a dense liquid that, upon dilution with water, furnished the guanidine as a solid. In certain cases where the guanidine was not a clear solid was subjected to column chromatography using an ether–hexane (1:1) system as the eluent. The above experimental conditions were adopted for other quaternaryammonium permanganates.



Scheme 1.

Table 1. Synthesis of guanidines using quaternaryammonium permanganate

No.	R	R^1	R^2	Yield[a] (%)		
				BTEAP	TBAP	CTMAP
1	Phenyl	*c*-C_6H_{11}	H	92	80	70
2	Phenyl	Ethyl	Ethyl	95	82	63
3	Phenyl	H	H	90	75	60
4	Phenyl	Benzyl	H	87	75	65
5	Phenyl	*n*-Butyl	H	86	70	56
6	*o*-Tolyl	H	H	82	72	55
7	Phenyl	*c*-C_6H_{11}	*c*-C_6H_{11}	82	60	50
8	Phenyl	*i*-Propyl	*i*-Propyl	78	65	50
9[b]	Phenyl	-$(CH_2)_2O(CH_2)_2$-	–	89	72	55
10[b]	2,6-Diethylphenyl	-$(CH_2)_2O(CH_2)_2$-	–	95	70	61

[a] Isolated yield.
[b] New compounds.[30]

Table 2. Melting points (uncorrected) of substituted guanidines (°C)

No.	1	2	3	4	5	6	7	8	9	10
Obs.	145–147	75–78	150–152	220–221	124–127	173–175	88–89	48–50	138–140	142–144
Lit.	143[26]	76–78[27]	148–150[28]	222–224[29]	127–129[29]	175–176[28]	86–87[27]	49–50[26]	–	–

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30. Spectral data of new compounds **9** and **10**
9. IR (cm^{-1}): 3348(s), 3174(s), 2358(m), 1321(s), 12121(s), 700(m), 656(m), 502(m). ^1H NMR (δ ppm, $CDCl_3$, 400 MHz): 7.3–6.8 (10H, Ar, m), 3.6 (4H, $-O(CH_2)_2$, t, $J = 4.72$ Hz), 3.3 (4H, $-N(CH_2)_2$, t, $J = 4.72$ Hz). ^{13}C NMR (δ ppm, $CDCl_3$, 100 MHz):[10] 150.5, 129.3, 127.2, 122.3, 65.5, 46.9. MS (m/e): 282 ($M^+ + 1$), 281 (M^+), 189, 145, 93, 77. Analysis: calcd for $C_{17}H_{19}N_3O$: C, 72.56; H, 6.80; N, 14.93. Found: C, 72.13; H, 7.01; N, 14.75. **10**. IR (cm^{-1}), 3325(s), 3251(s), 2930(m), 2335(m), 1563(s), 1485(s), 1231(s), 685(m), 525(m). ^1H NMR (δ ppm, $CDCl_3$, 400 MHz): 7.3–6.9 (7H, 6×Ar and 1×NH, m), 3.8–3.6 (4H, $-O(CH_2)_2$, t, $J = 4.68$ Hz), 3.5–3.4 (4H, $-N(CH_2)_2$, t, $J = 4.7$ Hz), 3.1–2.9 (12H, $4CH_3$, m), 1.6–2.0 (8H, $4CH_2$, m). ^{13}C NMR (δ ppm, $CDCl_3$, 100 MHz): 150.7, 144.7, 139.5, 135.5, 126.6, 67.6, 47.8, 25.1, 14.2. MS: 394 ($M^+ + 1$), 393 (M^+), 363, 306, 291, 248, 158. Analysis: calcd for $C_{25}H_{35}N_3O$: C, 76.29; H, 8.90; N, 10.73. Found: C, 76.25; H, 9.03; N, 10.58.