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An efficient multicomponent stereoselective synthesis of 1,2,4-trisubstituted 1,3-thiazetidines

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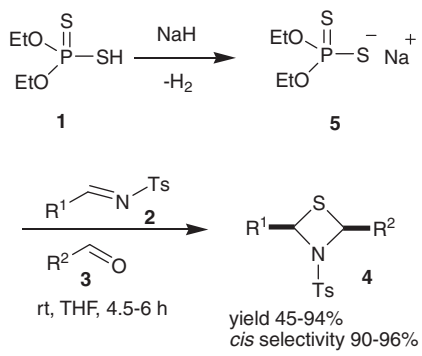
ABSTRACT

The first one-pot three-component coupling reaction of *O,O*-diethyl hydrogen phosphorodithioate, aldehydes, and aldimines affording 1,2,4-trisubstituted 1,3-thiazetidines is reported. The product is obtained in moderate to high yields (45–94%) and has excellent diastereoselectivity (90–96%) in favour of the cis isomer. Shorter reaction times, ambient temperature, operational simplicity, and high yields are the salient features of the present procedure.

In times where premium is put on speed, diversity, and efficiency in modern drug discovery processes,[1,2] multicomponent reaction (MCR) strategies offer significant advantages over conventional linear-type syntheses.[3–6] Various 1,3-thiazetidine derivatives are useful as broad spectrum antibacterial agents,[7a,b] commercial soil pesticides,[7c] and intermediates in the synthesis of thiazine sulfones,[7d] thiazolidines,[7e] triazoles, and triazines.[7f] Although 1,3-thiazetidines are pharmaceutically, agrochemically, and chemically relevant moieties,[7] limited efforts have been made for their synthesis. The construction of 1,3-thiazetidine ring system reported in the literature mainly includes photochemical rearrangement of 1,3-thiazines and their derivatives,[8] addition of aqueous methylamine saturated with hydrogen sulfide to formalin,[9] and cycloaddition of bis(trifluoromethy1)thioketene with Schiff bases,[10] isocyanates with carbodiimides,[11] and ethylene thiourea with aromatic aldehydes.[12] However, all of these reactions suffer from one or more disadvantages, such as expensive reagents, long reaction times, low yields, tedious work-up, and low selectivity. In continuation of our interest in developing new one-pot stereoselective cyclisation processes,[13–15] especially involving sulfur- and phosphorus-based leaving groups,[16–20] we report herein a conceptually new and convenient route to 1,2,4-trisubstituted 1,3-thiazetidines as outlined in Scheme 1.

After preliminary experimentation, it was found that the envisaged three-component synthesis was successful on treatment of *O,O*-diethyl hydrogen phosphorodithioate **1** with sodium hydride followed by aldimines **2** and aldehydes **3** to afford the target compounds 1,3-thiazetidines **4** in 45–94% yields (Scheme 1).[21] For comparison purpose, different solvents were tested in the present synthetic protocol and THF was found to be the best solvent amongst THF, benzene, and CH_3CN, in terms of yield and stereoselectivity. In order to investigate the scope of the substrate for general validity of the present investigation, several aldimines **2** and aldehydes **3** were used employing the present reaction conditions (Table 1). Isolation and purification by column chromatography afforded hitherto unreported target compounds **4** in 45–94% yields. The yield and diastereoselectivity were found to be consistently



Scheme 1. One-pot synthesis of 1,2,4-trisubstituted 1,3-thiazetidines **4**.

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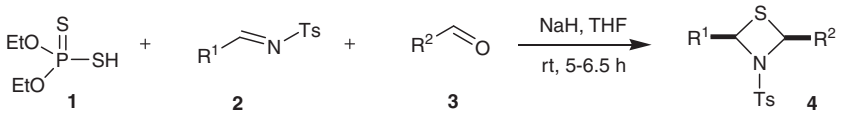
Table 1
One-pot synthesis of functionalised 1,3-thiazetidines **4** from diethyl hydrogen phosphorodithioate **1**, aldimines **2** and aldehydes **3**[a]



Entry	R^1	R^2	Time[b] (h)	Product **4**	Yield[c,d] (%)	Cis/trans[e] (%)
1	4-ClC_6H_4	Ph	6	**4a**	88	95:5[f]
2	2-ClC_6H_4	Ph	5	**4b**	89	97:3
3	4-$CH_3OC_6H_4$	Ph	5	**4c**	87	95:5
4	2-$CH_3OC_6H_4$	Ph	6	**4d**	88	96:4
5	4-ClC_6H_4	4-ClC_6H_4	4.5	**4e**	94	98:2
6	2-ClC_6H_4	4-ClC_6H_4	4.5	**4f**	93	97:3
7	4-$CH_3OC_6H_4$	4-ClC_6H_4	5.5	**4g**	89	95:5
8	2-$CH_3OC_6H_4$	4-ClC_6H_4	5	**4h**	90	95:5
9	4-ClC_6H_4	2-ClC_6H_4	4.5	**4i**	94	97:3
10	2-ClC_6H_4	2-ClC_6H_4	4.5	**4j**	91	96:4
11	4-$CH_3OC_6H_4$	2-ClC_6H_4	5	**4k**	89	95:5
12	2-$CH_3OC_6H_4$	2-ClC_6H_4	5.5	**4l**	90	96:4
13	4-$CH_3C_6H_4$	Ph	6	**4m**	85	95:5
14	Ph	4-$CH_3C_6H_4$	6	**4n**	80	96:4
15	4-ClC_6H_4	CCl_3	4.5	**4o**	91	95:5
16	*n*-Propyl	Ph	6	**4p**	45	95:5

[a] For experimental procedure, see Ref. 21.
[b] Stirring time at room temperature.
[c] Yield of isolated and purified product **4**.
[d] All compounds gave C, H and N analyses within ±0.38% and satisfactory spectral (IR, ^{1}H NMR, ^{13}C NMR and EIMS) data.
[e] As determined by ^{1}H NMR spectroscopy of the crude isolates.
[f] Cis/trans (%) after purification was 97:3.

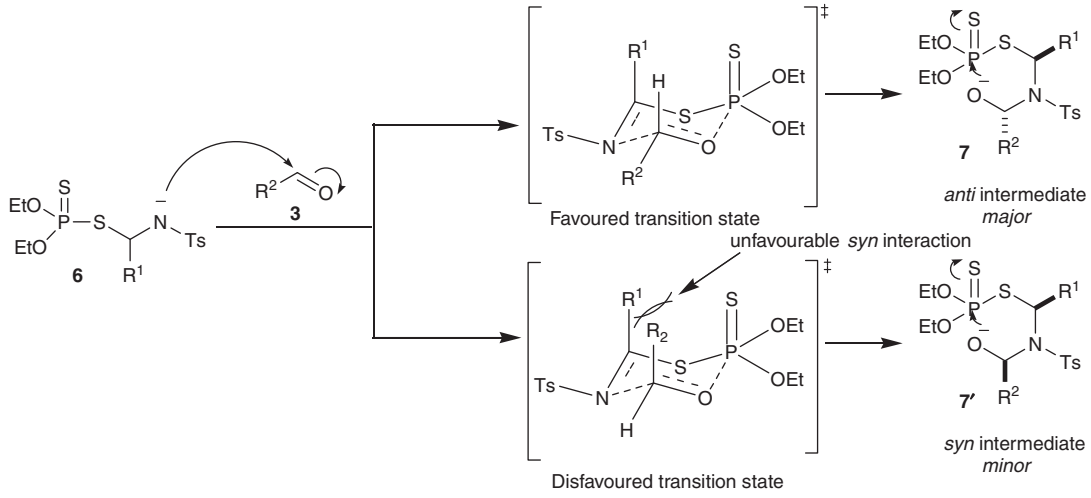
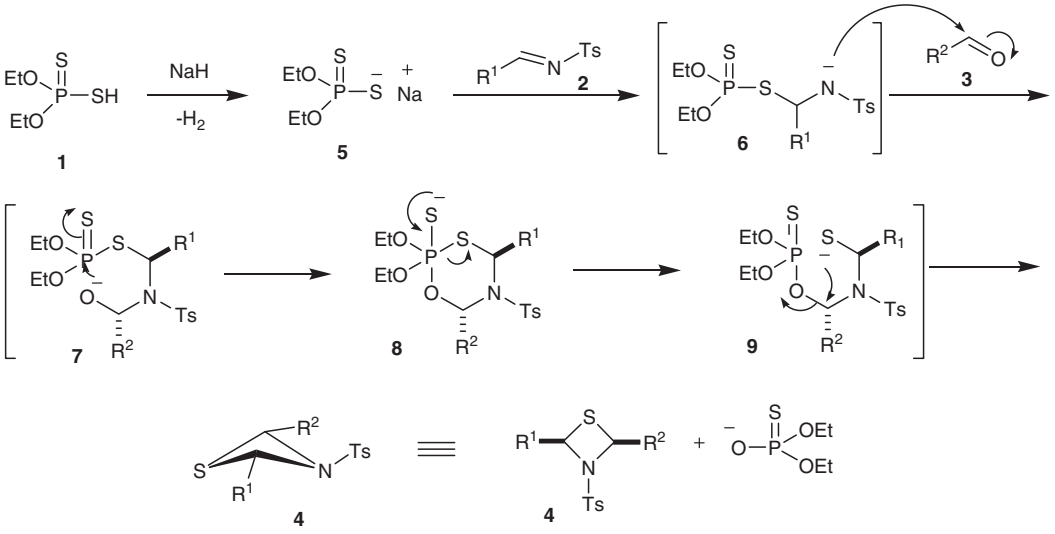


Figure 1. Transition state model for cis selectivity.

good (Table 1), the highest yield of the isolated and purified product **4** was 94% and the best diastereoselectivity was 96% as determined by ^{1}H NMR spectroscopy of the crude isolate in the case of **4e** (Table 1, entry 5). However, the present procedure with other carbonyl compounds, such as butanal, cyclohexanecarboxaldehyde, and acetophenone, does not give satisfactory results presumably because of the basic reaction conditions (yields of the corresponding products **4**: 21–28%). Both electron donating and electron withdrawing substituents in aldimines **2** as well as in aldehydes **3** are compatible to afford the corresponding products **4.** It was also realised that not only aromatic aldehydes but also an aliphatic non-enolizable aldehyde, for example, trichloroacetaldehyde works well in the present synthesis (Table 1, entry 15). It may be mentioned here that other groups like Boc and Cbz can also be used for activating nitrogen of the imine, but they are far less efficient than the tosyl group in terms of the yield of 1,3-thiazetidines **4**. It was also observed that an aldimine derived from an enolizable aldehyde afforded considerably lower yield of **4** (Table 1, entry 16). This is probably due to an easy α-deprotonation of the tautomerizable imine leading to several side reactions.

The formation of 1,3-thiazetidines **4** is highly diastereoselective in favour of the cis isomer. Presumably, the factors that control diastereoselectivity are the preference for placing substituents equatorially in six-membered transition states and the avoidance of *syn* interaction, respectively, as depicted in Fig. 1. The unfavoured *syn* transition state experiences steric interaction, thus the reaction proceeds through the more favourable transition state to form the *anti* configured intermediate **7**, stereoselectively leads to product **4** through **8** and **9**, successively with a high cis stereoselectivity via an S_N2 reaction involving an inversion of configuration of the relative stereocentre in **9** (Scheme 2).

The relative stereochemistry of 1,3-thiazetidines **4** was also established by NOE observations (Fig. 2). The strong NOE at 2-H upon irradiation of 4-H indicates that 2-H and 4-H are located on



Scheme 2. A plausible mechanism for the formation of 1,3-thiazetidines **4**.

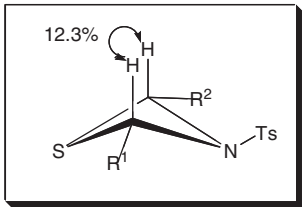


Figure 2. NOE observation.

the same face of the molecule, that is, 1,3-thiazetidines **4** have 3,5-cis configuration (Fig. 2). The reactions were clean and all the synthesised products were characterised by their ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopic data.

A plausible mechanism for the formation of 1,3-thiazetidines is depicted in Scheme 2. The treatment of *O*,*O*-diethyl hydrogen phosphorodithioate **1** with sodium hydride in THF at 60 °C generates sulfur anion **5** in situ which nucleophilically attacks at the aldimine carbon atom to give a nitrogen anion **6**. The anion **6** attacks aldehyde **3**, and the alkoxide ion **7** thus formed undergoes intramolecular cyclisation to afford the desired product **4** as depicted in Scheme 2. The high affinity of phosphorus to oxygen is the main driving force for the present heterocyclisation reaction (**7**→**4**, Scheme 2). Compounds **4** have potential to serve as intermediates of other compounds owing to their easy detosylation and opening of the 1,3-thiazetidine ring. Investigations on this subject are in our future plans and the results will be published elsewhere.

In summary, we have developed a convenient one-pot route for the synthesis of 1,3-thiazetidines in high yields and excellent diastereoselectivity. The synthesis utilises readily and widely available starting materials and is performed under ambient conditions. Thus, the present operationally simple and efficient methodology would be a practical alternative to the existing procedures for the synthesis of this kind of fine chemicals.

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21. *General procedure for the synthesis of 1,2,4-trisubstituted 1,3-thiazetidines* **4**: To a solution of *O*,*O*-diethyl hydrogen phosphorodithioate **1** (5 mmol) in dry THF (5 mL) was added dropwise a suspension of NaH (5 mmol) in dry THF (10 mL) with stirring at rt. After the addition was complete, and evolution of hydrogen gas (effervescence) had ceased, the reaction mixture was stirred at 60 °C for 30 min. Next, after cooling to rt, a solution of aldimine **2** (5 mmol) in dry THF (5 mL) was added, and the reaction mixture was stirred at rt for 1 h followed by the addition of aldehyde **3** (5 mmol) and stirring at rt for 3.5–5 h (Table 1). After completion of the reaction as indicated by TLC, 10% HCl (1 mL) was added and the mixture was stirred well. Then water (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to yield the crude product which was purified by silica gel column chromatography (hexane–EtOAc; 95:5) to give the corresponding thiazetidines **4**. The structure of the products was confirmed by their elemental and spectral analyses.
Physical data of representative compounds. Compound **4a**: White solid, yield 89%, mp 92–94 °C. IR (KBr) 3082, 2965, 2892, 2813, 2132, 1604, 1495, 1451, 753, 706 cm^{-1}. ^{1}H NMR (400 MHz; $CDCl_3$) δ: 2.46 (s, 3H, CH_3), 4.90 (s, 1H, 4-H), 4.92 (s, 1H, 2-H), 7.32 (d, 2H, J = 8.2 Hz, Ts), 7.61–7.72 (m, 5H, Ph), 7.64–7.69 (m, 2H, 4-ClPh), 7.74 (d, 2H, J = 8.3 Hz, Ts), 8.12–8.16(m, 2H, 4-ClPh). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.3, 57.4, 58.9, 126.1, 127.2, 128.4, 129.5, 130.7, 131.6,

132.4, 133.2, 134.8, 136.3, 138.9, 141.6. EIMS (*m/z*) 415 (M^+). Anal. Calcd for $C_{21}H_{18}ClNO_2S_2$: C, 60.64; H, 4.36; N, 3.37. Found: C, 61.01; H, 4.15; N, 3.07. Compound **4e**: White solid, yield 94%, mp 94–96 °C. IR (KBr) 3081, 2969, 2890, 2810, 2135, 1605, 1497, 1450, 756, 702 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$) δ: 2.44 (s, 3H, CH_3), 4.94 (s, 2H, 2-H, 4-H), 7.34 (d, 2H, *J* = 8.2 Hz, Ts), 7.62–7.70 (m, 4H, 4-ClPh), 7.76 (d, 2H, *J* = 8.1 Hz, Ts), 8.14–8.19(m, 4H, 4-ClPh). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.6, 57.1, 58.4, 126.4, 127.3, 128.3, 129.2, 130.2, 131.1, 132.5, 133.7, 135.7, 136.9, 138.0, 141.8. EIMS (*m/z*) 449 (M^+). Anal. Calcd for $C_{21}H_{17}Cl_2NO_2S_2$: C, 56.00; H, 3.80; N, 3.11. Found: C, 55.68; H, 3.53; N, 3.49.Compound **4i**: White solid, yield 91%, mp 91–93 °C. IR (KBr) 3084, 2969, 2894, 2814, 2134, 1601, 1492, 1452, 754, 706 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$) δ: 2.41 (s, 3H, CH_3), 4.94 (s, 1H, 4-H), 4.97 (s, 1H, 2-H), 7.31 (d, 2H, *J* = 8.3 Hz, Ts), 7.65–7.69 (m, 2H, 4-ClPh), 7.67–7.70 (m, 2H, 2-ClPh), 7.76 (d, 2H, *J* = 8.4 Hz, Ts), 8.10–8.15 (m, 2H, 2-ClPh), 8.12–8.16 (m, 2H, 4-ClPh). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.3, 48.1, 57.4, 102.9, 125.8, 126.9, 127.9, 129.0, 129.9, 130.8, 132.2, 133.5, 134.6, 135.9, 136.5, 137.3, 141.2. EIMS (*m/z*) 449 (M^+). Anal. Calcd for $C_{21}H_{17}Cl_2NO_2S_2$: C, 56.00; H, 3.80; N, 3.11. Found: C, 56.29; H, 3.50; N, 2.82. Compound **4o**: White solid, yield 91%, mp 84–87 °C. IR (KBr) 3081, 2969, 2890, 2813, 2134, 1605, 1497, 1450, 757, 702 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$) δ: 2.46 (s, 3H, CH_3), 4.81 (s, 1H, 4-H), 4.95 (s, 1H, 2-H), 7.37 (d, 2H, *J* = 8.2 Hz, Ts), 7.62–7.69 (m, 2H, 4-ClPh), 7.75 (d, 2H, *J* = 8.3 Hz, Ts), 8.10–8.17 (m, 2H, 4-ClPh). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.9, 56.4, 71.1, 101.5, 126.9, 128.4, 129.5, 130.8, 132.6, 136.5, 137.9, 142.4. EIMS (*m/z*) 415 (M^+). Anal. Calcd for $C_{16}H_{13}Cl_4NO_2S_2$: C, 42.03; H, 2.87; N, 3.06. Found: C, 41.81; H, 3.16; N, 3.26.