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Diastereoselective Cycloalkylation of Phosphoryl and Thiophosphoryl Acetonitriles by α,ψ-Dihalogenalkanes under Phase Transfer Catalysis Conditions

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ABSTRACT: *Cycloalkylation of phosphoryl and thiophosphoryl acetonitriles* **2** *by α,ψ-dihalogenalkanes was found to proceed diastereoselectively under phase transfer catalytic conditions yielding 1-(phosphoryl)-2-methyl-cycloalkane carbonitriles as trans-isomers with identical configuration of asymmetric cyclic carbon atoms ($R_C^*R_C^*$). In the case of additional asymmetric phosphorus atom in the starting substrate, trans-isomers are formed as a mixture of diastereomers differing in the configuration of the phosphorus atom ($S_P^*R_C^*R_C^*$ and $R_P^*R_C^*R_C^*$).* © 2006 Wiley Periodicals, Inc. Heteroatom Chem 17:13–21, 2006; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20186

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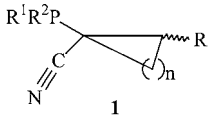
INTRODUCTION

Phosphine ligands having different functionalities in the molecule attract much attention due to their interesting chemical and complexing properties. Among functionalized phosphine ligands, those containing phosphorus- and nitrogen-complexing centers in a molecule (*P,N*-ligands) are of special interest showing high catalytic activity in many reactions [1]. Mostly such ligands contain the sp^3-(amine) or sp^2-(imine) hybridized nitrogen atom. A diversity of structural types of known *P,N*-ligands including the *sp*-hybridized nitrogen atom of the cyano function as an additional coordination site is not too wide. Nevertheless, they show interesting and diverse coordination behavior depending on the phosphine structure and nature of the metal [2]. Data concerning their usage in homogeneous catalysis are essentially limited by application of tris(β-cyanoethyl)phosphine in catalytic hydrophosphination [3], hydroformylation [4], alcohol carbonylation [5], etc.

Our attention was focused on cyano-substituted phosphine ligands with rather rigid stereochemical structure, which is advantageous for metal complex catalysis. In particular, we suggested that 1-(phosphino)cycloalkane carbonitriles **1** potentially

containing a few stereogenic centers in the molecule may be of interest for catalytic purposes.



1

n=1-4; R=H, Alkyl

Therefore, we elaborated a facile procedure for preparation of ligand precursors, namely (1-phosphoryl)cycloalkane carbonitriles (n = 1–3, R = H), comprising cycloalkylation of phosphorylacetonitriles by α,ω-dihaloalkanes under phase transfer catalytic conditions (PTC; K_2CO_3/DMSO, r.t.) [6]. It should be noted that this methodology allows one to obtain a wide pool of phosphorylated and thiophosphorylated compounds with ring size from three-membered one and larger in a good yield. Further, the reduction of the corresponding phosphoryl-containing precursors using trichlorosilane exemplified by 1-(diphenylphosphino)cyclopropane carbonitrile **1** (n = 1, R = H) was suggested as a convenient route to the target ligands [7]. Rhodium complexes formed by the above ligand and its analogues differing in the substituents at the phosphorus atom demonstrated nearly quantitative conversions in styrene hydroformylation at temperatures in the range of 70–100°C [8,9].

Therefore, for asymmetric metal complex catalysis, it was of interest to synthesize 1-(phosphino)cycloalkane carbonitriles **1** bearing an additional alkyl substituent R in the ring, for example methyl group, and therefore having at least two chiral centers (ring carbon atoms) in the molecule. In order to obtain the target compounds by the above reduction procedure, we first need to have their P=O precursors in hand. We suggested that cycloalkylation of phosphorylacetonitriles by α,ψ-dihalogenalkanes, i.e. α,ω-dihaloalkanes bearing additive methyl group at ω-position, should result in 1-(phosphino)-2-methyl cycloalkane carbonitriles as a statistical mixture of cis and trans isomers that differ by mutual disposition of methyl and phosphoryl groups relative the ring plane (Scheme 1).

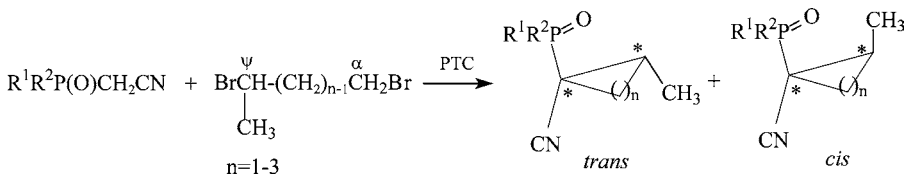
Furthermore, taking into account the further reduction, isomeric mixtures obtained might be further separated for individual isomers using the typical separation techniques, e.g. chromatography or fractional crystallization. We report herein the results of detailed investigation of such an interaction.

RESULTS AND DISCUSSION

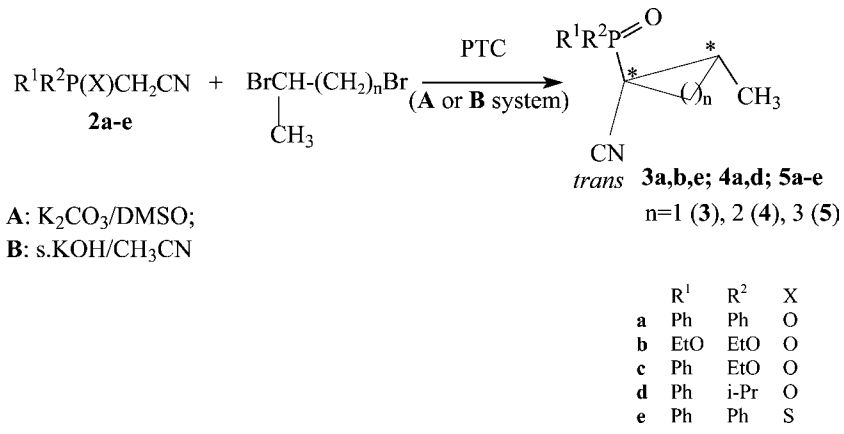
As we reported in our preliminary communication [10], the estimation of the full energies of both possible isomers for 1-(diphenylphosphoryl)-2-methylcyclopropane carbonitrile **3a** performed by ab initio calculations with full geometry optimization (B3LYP/6-31G*) using G98W software has revealed that the corresponding trans isomer was characterized by lower energy in comparison with the *cis*-**3a**. The energy win was 1.7 kcal/mol only and for reasons of statistics, such difference in energy should lead to the formation of the isomers in ca. 6:4 ratio. However, the interaction of diphenylphosphorylacetonitrile **2a** with α,ψ-dihaloalkanes unexpectedly turned out to proceed diastereoselectively, yielding only trans-isomers of cycloalkanes **3a, 4a, 5a** with the identical configuration of asymmetric carbon atoms ($R_C^*R_C^*$) and this result was unambiguously confirmed by X-ray analysis (Scheme 2). The compounds demonstrated a singlet in their ^{31}P-{^1H} NMR spectra and a single set of signals in the ^1H and ^{13}C spectra.

In order to estimate the generality of such diastereospecificity in this reaction, we involved in the interaction with α,ψ-dihaloalkanes a series of phosphorylacetonitriles **2b–e**. As in the case of **2a**, the reaction proceeded diastereoselectively for all compounds under investigation yielding the corresponding trans-isomers only.

Cycloalkylation was carried out at ambient conditions using K_2CO_3/DMSO as PTC system. At that, we used DMSO of two different grades: technical DMSO containing approximately 5% H_2O (further referred also as "wet" DMSO) and "dry" DMSO containing less than 0.1% H_2O (Fluka). In general, application of "wet" DMSO was preferable in terms of reaction rate in comparison with the dry one. Thus for the reactions with 1,3-dibromobutane and



SCHEME 1



SCHEME 2

1,4-dibromopentane yielding the *gem*-disubstituted butanes **4** and pentanes **5**, correspondingly, usage of wet DMSO leads to *ca*. 10-fold increase in the cycloalkylation rate (^{31}P NMR monitoring of reaction course). It fits well with the known fact that the amount of water in the organic phase used in the PTC reactions often sufficiently influences the process rate (participation of so called "omega phase") [11]. Nevertheless, it should be noted that excluding the interaction of the least sterically hindred substrate **2b**, phosphorylated cyclopropanecarbonitriles **3** are not formed in reasonable yields under "wet" DMSO (Table 1).

As one could expect, the appearance of additional steric hindrances in an electrophilic component, i.e. changing α,ω-dihaloalkanes for α,ψ-derivatives, leads to the drastic decrease in the cycloalkylation rate [12]. Thus, cycloalkylation of diphenylphosphorylacetonitrile **2a** by 1,2-dibromoethane is completed over ca. 20 h at room temperature to give the corresponding cyclopropane in ~70% yield [6a]. For comparison, in the reaction of the same substrate **2a** with 1,2-dibromopropane, the yield of 2-methyl-cyclopropane carbonitrile **3a** obtained for the same period of time is only 2%. The yield of **3a** was increased up to 55% using the dry DMSO after 16 days of stirring. Under other conditions being equal, less sterically hindered *gem*-disubstituted butanes **4** and pentanes **5** are formed more easily and in higher yields in comparison with the corresponding cyclopropanes **3**.

Furthermore, the reaction is very sensitive to steric hindrances at the phosphorus atom and all other conditions being equal, the reaction rate

TABLE 1 Dependence of the Cycloalkylation Rate and Yields of **5–7** on the PTC System in Use

Compound	*R^1R^2*	*X*	*n*	*Interphase System*[a]	*Reaction Time (h)*	*Yield of Cycloalkane (%)*[b]
3a	Ph_2	O	1	$\mathbf{A_1}$	380	55
				$\mathbf{A_2}$	20	2
3b	$(EtO)_2$	O	1	$\mathbf{A_2}$	40	50
3d	Ph(Pr-i)	O	1	$\mathbf{A_1}$	300	<1
3e	Ph_2	S	1	$\mathbf{A_2}$	40	<1
				B	2,5	43
4a	Ph_2	O	2	$\mathbf{A_1}$	312	80
				$\mathbf{A_2}$	20	75
4d	Ph(Pr-i)	O	2	$\mathbf{A_1}$	336	45
5a	Ph_2	O	3	$\mathbf{A_1}$	192	87
				$\mathbf{A_2}$	20	82
5b	$(EtO)_2$	O	3	$\mathbf{A_2}$	30	70
5c	Ph(EtO)	O	3	$\mathbf{A_2}$	20	96
5d	Ph(Pr-i)	O	3	$\mathbf{A_1}$	192	50
5e	Ph_2	S	3	$\mathbf{A_2}$	37	32
				B	7,5	100

[a]PTC system: $\mathbf{A_1}$ = K_2CO_3/dry DMSO; $\mathbf{A_2}$ = K_2CO_3/wet DMSO; **B** = KOH/CH_3CN.
[b]According the ^{31}P NMR data of the reaction mixture.

decreased in the series $(EtO)_2P(O)$ > $Ph(EtO)P(O)$ > $Ph_2P(O)$ ≫ $Ph(i\text{-}Pr)P(O)$ > $Ph_2P(S)$. In the series of phosphorylacetonitriles, yield of the cyclopropane **3d** bearing phenyl and isopropyl substituents was less then 1%.

Moreover, as thiophosphorylacetonitriles possess higher CH-acidity comparing with their phosphoryl analogues, their cycloalkylation by α,ω-dihaloalkanes proceeds approximately two times faster with using the system K_2CO_3/DMSO [6b]. At the same time in the reaction of diphenylthiophosphorylacetonitrile **2e** with α,ψ-dihaloalkanes, we failed to obtain the satisfactory yields of the desired cycloalkanes using the above "mild" heterogeneous system. Taking into account that thiophosphorylacetonitrile carbanions are rather stable under more severe conditions [13], we succeeded to carry out cycloalkylation of **2e** by α,ψ-dibromoalkanes using solid KOH as a base in acetonitrile solution [14]. As in these cases, we obtained thiophosphoryl-substituted cycloalkanecarbonitriles **3e, 5e** as trans-isomers only, one may conclude that the stereochemical result does not depend on the interphase system in use.

It should be noted that the formation of the corresponding monoalkylated products generated at the first step of cycloalkylation was observed by NMR technique [15] only at the reaction of (isopropyl)phenylphosphorylacetonitrile **2d**, apparently the most sterically hindered substrate among those with phosphoryl group, with 1,3-dibromobutane. The ratio of the target cycloalkane and monoalkylated product was ca. 7:3. In other cases, the rate of secondary alkylation exceeds that for the first alkylation step which is similar to regularity observed for cycloalkylation by α,ω-dihaloalkanes where the rates of the primary and secondary alkylation are comparable [9].

If the phosphorus atom in a starting substrate is the asymmetric one (**2c,d**), the resulting cycloalkanes **4d, 5c,d** have already three asymmetric atoms, namely two ring carbon atoms and the phosphorus one. As cycloalkylation does not affect the phosphorus atom during the reaction course, as expected in these cases, the final products were obtained as a statistical mixture of two diastereomers **A** and **B** distinguished in the configuration of the phosphorus atom (**A**: $R_P{}^*R_C{}^*R_C{}^*$ and **B**: $S_P{}^*R_C{}^*R_C{}^*$). This fact was confirmed by X-ray analysis carried out for both isomers of cyclopentane **5d** (R′ = Ph, R″ = *i*-Pr, $n = 3$), which were resolved by fractional crystallization after chromatography purification.

In order to explain the diastereoselective reaction course and in view of the fact that cycloalkylation would proceed in two stages, one may assume that monoalkylated product was formed as statistic mixture of diastereoisomers having the identical or the opposite configuration of the chiral carbon atoms ($R_C{}^*$, $R_C{}^*$ and $R_C{}^*S_C{}^*$). The second reaction stage of intramolecular cyclization proceeds via the formation of a flat carbanion with degeneration of asymmetry at the α-carbon atom. In other words, no matter how the first stage proceeds stereochemically, the whole stereochemical result is determined by the cyclization step only. Apparently, for steric reasons, the rate of cyclization leading to the formation of the cis isomer (v_{2cis}) is very low (the high energy barrier) while the rate of trans-isomer formation (v_{2trans}) is rather high. Therefore, the above trans isomer presents apparently the product of kinetic control of the second reaction step.

The structures of all the compounds obtained were confirmed by IR and NMR spectral data (Tables 2 and 3) along with X-ray investigations carried out for a few substances with different cyclic sizes. In the IR spectra, the single characteristic absorption band of CN group is observed at 2225–2233 cm^{-1}. For the products having P=O moiety, the $\nu_{P=O}$ absorption band normally changes its position from 1196 cm^{-1} up to 1258 cm^{-1} depending on the amount of P–C bonds at the phosphorus atom. Positions of P=S band at 653 and 658 cm^{-1} for compounds **3e** and **5e** correspondingly were identified via the Raman spectroscopy. Moreover, the sharp characteristic bands at 1436–1438 cm^{-1} corresponding to deformation oscillations of CH_2 group were observed in the IR spectra.

In the $^{31}P\text{-}\{^1H\}$ NMR spectra of **3a,b,e, 4a, 5a,b,e** bearing the identical substituents R^1, R^2 at the phosphorus atom, singlet signals were observed in a region typical for the particular environment. Chemical shifts of trans **3–5** in the ^{31}P NMR spectra are slightly different from those of their analogues without methyl substituent in the ring [9], and the cyclic size practically does not influence the position of the signal. For compounds **4d, 5c,d** having different substituents R^1, R^2, isomers **A** and **B** demonstrate two closely located signals in the $^{31}P\text{-}\{^1H\}$ NMR spectra. The comparison of NMR and X-ray data for both diastereoisomers of **5d** revealed that the signal of isomer **A** ($R_P{}^*R_C{}^*R_C{}^*$) with identical configuration of all chiral centers in the molecule is downfield shifted in comparison with that of the second isomer **B** ($S_P{}^*R_C{}^*R_C{}^*$). Assuming that such dependence should have a general character, the signals for the compounds **4d** and **5c** in the NMR spectra were assigned in a similar way.

The general pattern characteristic for the ring carbon atoms in the series of 1-(thio)phosphorylcycloalkane carbonitriles [9] is kept in the signal

TABLE 2 Physicochemical, Elemental Analysis, and IR Data for Compounds **3–5**

Compound	Yield after Purification (%)	PTC System in Use	mp (°C) or bp (°C/mm Hg)	Formula	Found (%) / Calculated (%) C	H	N	P	IR, ν (cm⁻¹) P=O	CN	CH_2
3a	37	**A**$_1$	101–103 (CH_2Cl_2–petroleum–ether)	$C_{17}H_{16}NOP$	72.65 / 72.59	5.78 / 5.73	4.97 / 4.98	–	1211	2226	1436
3b	29	**A**$_2$	100–105 (1 mm Hg)	$C_9H_{16}NO_3P$*	49.71 / 49.77	7.36 / 7.42	–	14.04 / 14.26	1267	2235	1444(br)
3e	31	**B**	89–90 (Et_2O)	$C_{17}H_{16}NPS$	68.79 / 68.67	5.49 / 5.42	4.77 / 4.71	–	653[a]	2229	1434
4a	62	**A**$_2$	92-94[b]	$C_{18}H_{18}NOP$	73.44 / 73.21	6.13 / 6.14	4.42 / 4.53	–	1199	2226	1438, 1435
4d[c]	28	**A**$_1$	Oil[b]	$C_{15}H_{20}NOP$	69.12 / 68.95	7.58 / 7.71	–	11.54 / 11.85	1199	2223	1438
5a	50	**A**$_2$	123–124 (petroleum-ether)	$C_{19}H_{20}NOP$	72.61 / 73.77	6.46 / 6.52	4.42 / 4.53	–	1212, 1196	2226	1438
5b	64	**A**$_2$	Oil[b]	$C_{11}H_{20}NO_3P$	53.45 / 53.87	8.03 / 8.22	–	12.27 / 12.63	1258	2233	1450(br)
5c[c]	69	**A**$_2$	Oil[b]	$C_{15}H_{20}NO_2P$	64.72 / 64.97	6.93 / 7.27	–	–	1238	2231	1439
5d-A	16	**A**$_1$	141–143[d]	$C_{16}H_{22}NOP$	69.44 / 69.80	8.30 / 8.05	4.70 / 5.09	–	1187	2222	1438
5d-B	13	**A**$_1$	74–76[d]	$C_{16}H_{22}NOP$	69.56 / 69.80	7.85 / 8.05	4.95 / 5.09	–	1185	2222	1436
5e	76	**B**	65–66 (Et_2O)	$C_{19}H_{20}NPS$	70.11 / 70.13	6.09 / 6.19	4.27 / 4.30	–	658[a]	2230	1436

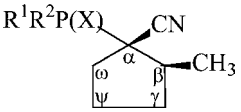
[a] $\nu_{P=S}$ (Raman).
[b] Purified by column chromatography (petroleum ether: acetone=10:3).
[c] Obtained after chromatography as a mixture of two isomers **A**($R_P^* R_C^* R_C^*$) and **B** ($S_P^* R_C^* R_C^*$) in the following ratio: **4d-A**:**4d-B** = 75:35; **5c-A**: **5c-B** = 55:45.
[d] Fraction containing **A** and **B** isomers in ca. 48:45 ratio from column chromatography step (petroleum ether: acetone = 10:3) was evaporated to dryness, then resuspended in Et_2O (twice); the precipitate filtrated presented **5dA** isomer, while **5dA** was obtained as a result of filtrate evaporation.

disposition in the ^{13}C NMR spectra of **3–5**. Thus, for cyclopropanes **3**, the chemical shift of tertiary carbon atom is significantly upfield shifted in comparison with those in the compounds with larger cyclic size; the value of $^1J_{PC}$ in **3** is much larger than the value of direct coupling constants in the corresponding cyclobutanes **4** and cyclopentanes **5**. Naturally, the value of $^1J_{PC}$ of the particular compound is determined by the nature of the substituents at the phosphorus atom and $^1J_{PC}$ coupling constant is always less for the thiophosphorylated derivatives when compared with their analogues with the P=O group [9]. Also, it should be noted that the signal of CH_3 group carbon atom is slightly downfield shifted in **4** and **5** in comparison with cyclopropanes **3**.

In the ^1H NMR spectra, the signal of the methyl substituent appears as a characteristic doublet in the range 0.48–1.56 ppm ($^3J_{HH}$ = 6.0–7.3 Hz). Here a spin–spin interaction is observed only with a geminal proton and there is no spin–spin coupling at phosphorus. For the series of the compounds with the same phosphorus moiety, the signal of the methyl group is upfield shifted with the increase of the cycle size, e.g. for compounds with diphenylphosphoryl group $\delta(CH_3)$ is equal to 1.41 ppm for 2-methylcyclopropane **3a**, 0.88 ppm for cyclobutane **4a**, and 0.80 ppm for 2-methylcyclopentane **5a**. Also, it may be noted that the value of the chemical shift of the methyl substituent of **A**-$R_P^* R_C^* R_C^*$-isomers of **4d, 5c,d** exceeds that of the **B**-$S_P^* R_C^* R_C^*$ isomer and $^3J_{HH}$ is generally higher in the case of the **A**-isomer.

As mentioned above, the X-ray diffraction (XRD) study was carried out for single crystals of the representative compounds **3a, 4a, 5d-A, 5d-B,** and **5e** differing both in the cyclic size and substituents at the phosphorus atom. According to these data, the products obtained are the trans-isomers with respect to the disposition of either phosphoryl or thiophosphoryl group and the methyl substituent relative to the ring average plane of the cycle (Fig. 1, racemic mixtures, identical configuration of the ring chiral centers $R_C^* R_C^*$). Similar values of chemical shifts for all compounds obtained in ^{31}P-{^1H} NMR spectra, the similarity in the shift values for the methyl group, and in the multiplicity of the signals for all the cycloalkanes in ^1H and ^{13}C NMR spectra

TABLE 3 Selected ^{1}H, ^{31}P, and ^{13}C NMR Parameters for **3–5**



Compound	^{31}P NMR δ_P, ppm	^{1}H NMR Spectrum (δ (ppm), J (Hz), $CDCl_3$)[a] δCH_3, d ($^{3}J_{HH}$)	δCH (m)	δCH_2	^{13}C NMR Spectrum (δ (ppm), J (Hz), $CDCl_3$)[a] δC^{α}, d ($^{1}J_{PC}$)	δC^{β} ($^{2}J_{PC}$)	δC^{ω}	δC^{ψ}	δC^{γ}	δCH_3	δCN, d($^{3}J_{PC}$)
3a	28.80	1.41 (6.1)	2.07–2.18	1.26–1.34 m (1H) 1.89–1.96 m (1H)	13.74 (99.2)	20.12	20.89	–	–	14.92	118.84 (9.9)
3b	19.43	1.27 (6.0)	1.70–1.81	1.08–1.13 m (1H) 1.55–1.62 m (1H)	14.60 (141.0)	19.09 (1.2)	19.90	–	–	13.43	116.01 (4.5)
3e	51.06	1.44 (6.0)	2.13–2.24	1.26–1.32 m (1H) 1.96–2.03 m (1H)	14.91 (77.3)	20.42	21.12	–	–	14.57	118.9 (5.4)
4a	28.10	0.88 (6.9)	3.17–3.29	1.92–2.03 m (1H) 2.19–2.29 m (2H) 2.80–2.98 m (1H)	41.03 (70.7)	33.35 (2.5)	24.01 d ($^{2}J_{PC}$ 2.48)	26.98 (12.7)	–	18.22	120.06 (5.0)
4d-A	44.00	1.56 (7.3)	3.10–3.32	1.86–2.08 m (2H) 2.24–2.55 m (2H)	38.92 (73.0)	33.53 (2.9)	24.93	26.32 (12.9)	–	18.27	119.92
4d-B	42.81	1.27 (6.8)	3.46–3.53	[b]	39.94 (68.5)	33.84	25.02	27.83 (13.4)	–	17.27	119.95
5a	28.00	0.80 (6.8)	2.69–2.91	1.39–1.57 m (1H) 1.74–1.89 m (2H) 1.95–2.21 m (2H) 2.43–2.64 m (1H)	46.10 (70.1)	38.89	35.84	35.13 (6.78)	23.90 (5.27)	17.43	121.00 (2.3)
5b	22.71	0.98 (6.8)	2.11–2.18	1.11–1.24 m, 1H 1.41–1.51 m (1H) 1.53–1.65 m (1H) 1.66–1.73 m (1H) 1.90–2.07 m (2H)	49.35 (73.6)	39.39	34.32	33.08 (11.8)	22.30 (9.2)	15.74	117.49 (4.9)
5cA	37.99	1.31 (7.2)	2.65–2.76	1.16–1.36 m (1H) 1.72–1.78 m (2H) 1.78–1.84 m (1H) 1.86–2.02 m (1H) 2.20–2.29 m (1H)	45.65[c] (103.7)	38.05	33.72	32.30 (9.1)	21.96 (8.6)	15.68	118.02
5cB	37.23	0.67 (6.8)	2.52–2.63	1.42–1.51 m (1H) 1.60–1.75m (2H) 1.92–2.04 m (1H) 2.03–2.14 m (1H) 2.30–2.39 m (1H)	45.65 (103.7)	38.16	33.80	33.48 (9.2)	22.55 (6.4)	15.99	118.10
5dA	46.21	1.35 (7.3)	2.80–2.93	1.47–1.58 m (1H) 1.63–1.73 m (2H) 1.80–1.88 m (1H) 1.93–2.05 m (2H)	45.17 (61.0)	37.87	37.22	35.01 (4.7)	23.67 (5.3)	15.68 d ($^{3}J_{PC}$ 3.9)	121.05 (2.4)
5dB	44.23	0.48 (6.4)	2.78–2.91	1.64–1.75 m (1H) 1.80–1.91 m (2H) 1.94–2.03 m (1H) 2.67–2.38 m, 2H)	37.56 (63.9)	39.90	35.87	34.79 (6.2)	24.76 (4.10)	17.10	120.84 (3.2)
5e	54.78	0.70 (6.8)	2.83–2.97	1.44–1.54 m (1H) 1.71–1.89 m (2H) 1.95–2.03 m (1H) 2.19–2.28 m (1H) 2.63–2.74 m (1H)	47.32 (51.1)	40.37 d ($^{2}J_{PC}$ 2.4)	37.23 ($^{2}J_{PC}$ 2.2)	34.79 (8.0)	23.83 (6.2)	17.10	120.96

[a]Chemical shifts for R^1 and R^2 substituents which are situated at typical characteristic areas are omitted for clarity.
[b]Overlapping with CH_2 signals of the major isomer **A**.
[c]Overlapping of C^1 signals for both isomers.

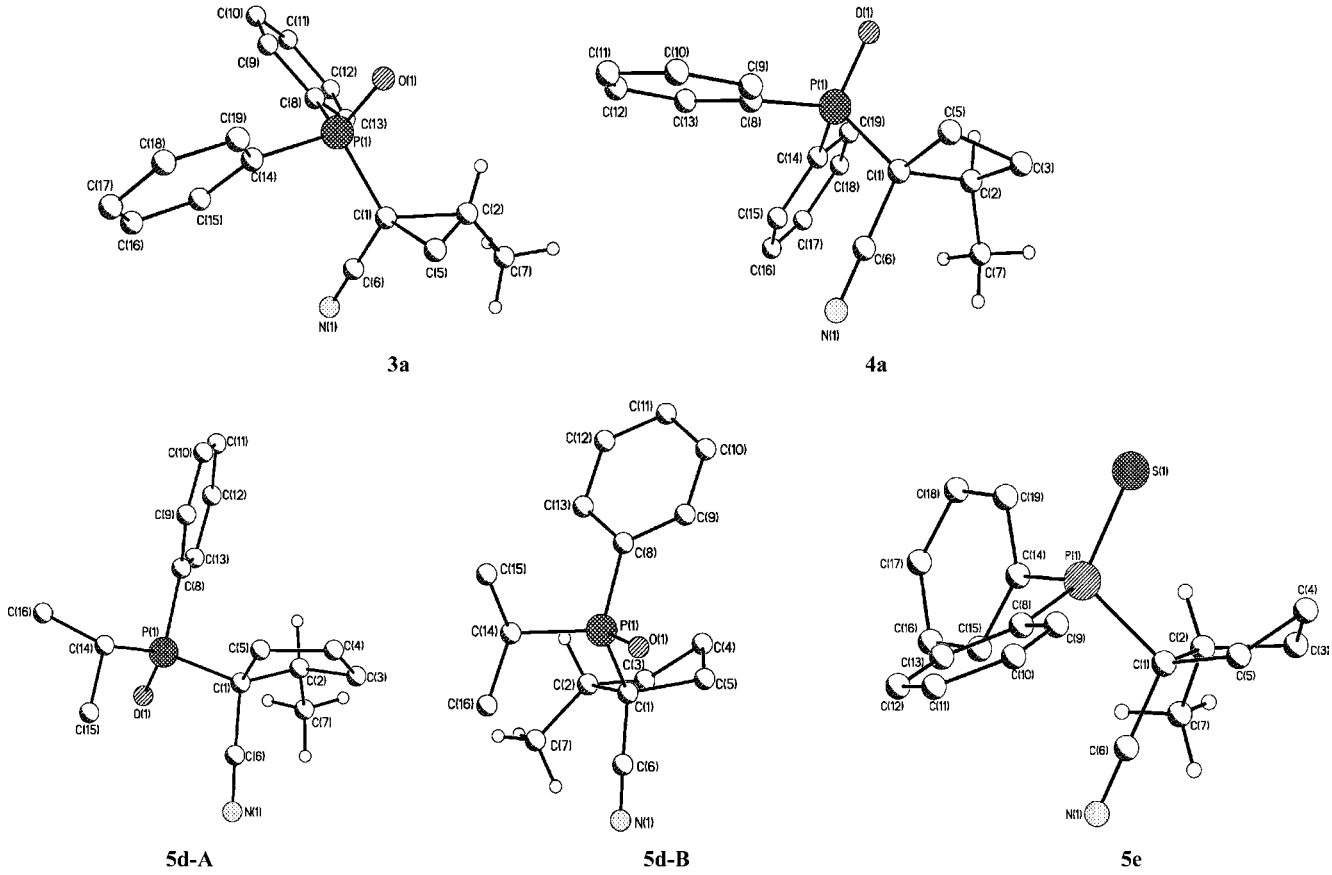


FIGURE 1 The general view of **3a**, **4a**, **5d-A**, **5d-B**, and **5e**.

TABLE 4 Selected Bond Lengths (Å) and Torsion Angles (deg) for Some Representatives of *gem*-Disubstituted Cycloalkanes **3–5**

	3a	**4a**	**5d-A**	**5d-B**	**5e**
P(1)–X(1)[a]	1.488(2)	1.481(1)	1.482(2)	1.471(2) Å	1.962(1)
P(1)–C(1)	1.819(2)	1.839(2)	1.864(2)	1.870(3) Å	1.899(3)
P(1)–C(8)	1.803(2)	1.793(2)	1.804(3)	1.816(3)	1.819(3)
P(1)–C(14)	1.798(2)	1.800(2)	1.812(2)	1.791(3)	1.820(3)
X(1)P(1)C(1)C(6)	177.3	175.7	45.8	49.8	160
P(1)C(1)C(2)C(7)	144.6	105.4°	71.8	170.0	109.2
X(1)P(1)C(2)C(7)			87.8	5.6	155.2
Conformation (dev)		Bended along C(2)···C(5) line	Distorted envelope C(2)	Distorted envelope C(4)	Distorted envelope C(4)

[a]X = O(1) for **3a**, **4a**, **5d-A**, **5d-B**, and S(1) for **5e**.

allowed us to assert that they present the trans-isomers too.

Principal geometrical parameters of **3a, 4a, 5d-A, 5d-B**, and **5e** that are closed to the expected values are listed in Table 4. According to XRD, all compounds crystallize as racemates excluding the diastereomer **5d-B** ($S_P{}^*R_C{}^*R_C{}^*$). The latter crystallizes as conglomerate (mechanical mixture of homochiral crystals) in the chiral space group ($P2_12_12_1$) and hence crystal induced spontaneous resolution is observed in this particular case. Unfortunately, the Flack parameter [16] for **5d-B** is equal to 0.4 indicating the presence of the so-called lamellar racemic twining that can be a serious obstacle for the resolution of enantiomers by crystallization (see [17]).

In the crystal structures of **3a**, **4a**, and **5e** bearing diphenylphosphoryl or diphenylthiophosphoryl substituent, both P=O and P=S groups are characterized by the antiperiplanar orientation with respect to the cyano group, while in the case of both isomers of **5d** (**A** and **B**) with the isopropyl(phenyl)phosphoryl moiety the synclinal orientation of the P=O and CN groups is observed. Besides the difference in the phosphorus atom configuration, the envelope conformation of the five-membered cycles in **5d-A** and **5d-B** isomers is distinguished by the carbon atom deviating from the ring plane.

To summarize the results, the interaction of phosphoryl- and thiophosphoryl-acetonitriles **2** with α,ψ-dihaloalkanes proceeds according to the cycloalkylation scheme to give 1-(phosphoryl)-2-methyl-cycloalkane carbonitriles as trans-isomers with the identical configuration of asymmetric cyclic carbon atoms independently on the substituents at the phosphorus atom and of PTC system in use.

EXPERIMENTAL

General

NMR spectra were recorded on a "Bruker WP-200SY," "DPX-200," and "AMX-400" spectrometers in $CDCl_3$ solutions using residual proton signal or the characteristic ^{13}C chemical shift of the deutero solvent as an internal standard (^1H or ^{13}C, respectively) and 85% H_3PO_4 (^{31}P) as an external standard. IR spectra were recorded in KBr pellets on a Fourier-spectrometer "Magna-IR750"(Nicolet), resolution 2 cm^{-1}, 128 scans.

Synthesis of (1RS,2RS)-1-(Phosphoryl)-2-methyl-cycloalkane Carbonitriles **3–5** *(General Procedure).* The mixture of the corresponding phosphorylacetonitrile **2a–d** (4.15 mmol), K_2CO_3 (2.30 g, 16.60 mmol) and 8.3 mmol of the corresponding α,ψ-dibromoalkane in DMSO (40 mL) was stirred at the ambient temperature during the time given in Table 1 (^{31}P monitoring of the reaction course). Then the mixture was diluted by water (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). In the case wherein the reaction is not completed (the initial phosphorylacetonitrile **2** still remains in the reaction mixture), it is preferable to extract first the reaction mixture with Et_2O followed by the extraction with CH_2Cl_2, as this allows us to separate the product (Et_2O layer) from the remaining starting compound extracted by CH_2Cl_2. The organic layers were washed by water (2 × 30 mL), dried over $MgSO_4$, and evaporated

TABLE 5 Crystal Data and Structure Refinement Parameters for **3a, 4a, 5d-A**, **5d-B,** and **5e**

Compound	**3a**	**4a**	**5d-A**	**5d-B**	**5e**
Empirical formula	$C_{17}H_{16}NOP$	$C_{18}H_{18}NOP$	$C_{16}H_{22}NOP$	$C_{16}H_{22}NOP$	$C_{19}H_{20}NPS$
M	281.28	295.30	275.32	275.32	325.39
T (K)	100(2)	100(2)	120(2)	120(2)	173(2)
Diffractometer	Smart 1000 CCD	Smart 1000 CCD	Smart 1000 CCD	Smart 1000 CCD	Syntex $P2_1$
Crystal system	Orthorhombic	Triclinic	Orthorhombic	Orthorhombic	Triclinic
Space group	*Aba*2	*P*-1	$Pna2_1$	$P2_12_12_1$	*P*-1
a (Å)	23.103(7)	7.602(3)	14.220(3)	10.345(3)	7.880(3)
b (Å)	15.708(3)	10.182(4)	9.973(2)	11.073(4)	9.435(5)
c (Å)	8.187(1)	11.042(5)	11.009(2)	13.671(4)	12.551(6)
α (°)		87.526(9)			74.87(1)
β (°)		79.305(9)			83.60(1)
γ(°)		68.676(9)			67.92(1)
V (Å^3)	2971.0(11)	782.0(6)	1561.3(5)	1566.1(8)	834.7(7)
Z(Z')	8(1)	2(1)	4(1)	4(1)	2(1)
F(000)	1184	312	592	592	344
D_{calc} (g cm^{-1})	1.258	1.254	1.171	1.168	1.295
μ (cm^{-1})	1.80	1.740	1.69	1.69	2.86
Scan type	ω	ω	ω	ω	θ/2θ
$2\theta_{max}$(°)	60.0	58.0	60.0	52.0	52.0
Refl. measured	11516	6218	16663	9294	3613
Independent refl. [R_{int}]	4242 [0.0260]	4103 [0.0221]	4535[0.0481]	3067 [0.0410]	3127[0.0270]
Observed refl.	3434	3039	2401	2213	2167
Parameters	237	262	176	175	200
Flack parameter	0.0(1)		0.00(5)	0.44(14)	
$R_1(F_{hkl})$	0.0489	0.0531	0.0526	0.0528	0.0596
wR_2	0.1118	0.1364	0.1165	0.1015	0.1307
GOF	1.091	0.964	0.967	1.051	1.049
ρ_{max}/ρ_{min}(eÅ^{-3})	0.354/−0.197	0.481/−0.335	0.406/−0.169	0.310/−0.188	0.473/−0.393

to dryness. The residue was purified by crystallization (petroleum ether/CH_2Cl_2 = 90/10), column chromatography (SiO_2, gradient hexane-acetone from 100:1 to 100:20), or distillation in vacuo, as appropriate.

Synthesis of (1RS, 2RS)-1-(Thiophosphoryl)-2-methylcycloalkane Carbonitriles **3e, 5e** *(General Procedure).* To a stirred mixture of diphenylthiophosphorylacetonitrile **2e** (4.15 mmol) and 2 eq. of the corresponding α,ψ-dibromoalkane (8.3 mmol) in CH_3CN (~25 mL), the catalytic amount of triethylbenzylammonium chloride (TEBA) was added followed by portionwise addition of powdery KOH (8.3 mmol) over 10 min. The mixture was further stirred 3 h, then evaporated to reduced volume. Water was added to the residue, and the mixture was extracted by CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried over Na_2SO_4 and filtered, and a filtrate was evaporated to dryness and purified by recrystallization from Et_2O.

X-Ray Crystallography

The structures **3a, 4a, 5d-A, 5d-B**, and **5e** were solved by the direct method and refined by the full-matrix least squares against F^2 in an anisotropic approximation for no-hydrogen atoms. Crystal data and structure refinement parameters for **3a, 4a, 5d-A, 5d-B**, and **5e** are given in Table 5. All calculations were performed using the SHELXTL software [18]. The crystallographic data have been deposited with the Cambridge Crystallographic Data Center, CCDC 196045 for **3a**, CCDC 196046 for 4**a**, CCDC 280985 for **5e**, CCDC 280986 for **5d-A** and CCDC 280987 for **5d-B**. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

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[14] It should be noted that usage of KOH/CH_3CN system in order to increase the yields of the cyclic products is unsuitable for phosphorylacetonitriles **2a–d** undergoing essentially P—C cleavage under such conditions.

[15] Introduction of alkyl substituents to the central carbon atom in the (thio)phosphorylacetonitrile results in the successive downfield shifting of the signal in the ^{31}P NMR spectra; at that, the signal of the cycloalkylation product is downfield shifted when compared with dialkylated product having a linear structure, see [6c].

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