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Pd-catalysed amidation of 2,6-dihalopurine nucleosides. Replacement of iodine at 0 °C

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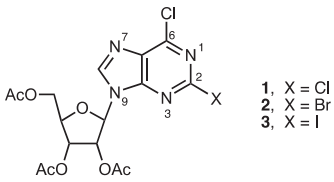
ABSTRACT

Pd-catalysed reactions of 2-Cl, 2-Br and 2-I derivatives of a 6-chloropurine nucleoside with benzamide have been compared, using Pd_2dba_3, Xantphos and Cs_2CO_3 in toluene, between 20 and 80 °C. The reactivity order was 2-I > 2-Br > 6-Cl ≫ 2-Cl. The 2-I substituent could be replaced even at 0 °C, under conditions disclosed here for the first time. On the other hand, the replacement of the chlorine atom at position 2 (2-Cl) required 110 °C.

In spite of the remarkable advances in transition metal-catalysed cross-coupling reactions for the formation of carbon–carbon and carbon–heteroatom bonds in heterocycles and nucleosides,[1] there continues to be an increasing demand of new improvements. Control of the cross couplings of dihalo or trihalo derivatives of purines and their nucleosides with nucleophiles has interest because of the biological or medicinal significance of the resulting products. In particular, selective substitutions can provide alternative routes to the analogues and surrogates of purine-derived known anticancer agents[2] and, in general, to adenosine receptor agonists or antagonists.[3]

In the past years we have been interested in ring modifications of nucleosides, aimed at preparing endo and exo ^{15}N-labeled samples. Ring nitrogen labels were introduced by means of new ring-opening–ring-closing reactions, while exocyclic labels came from Buchwald–Hartwig amidation reactions of chloropurine nucleosides with [^{15}N]benzamide.[4] In this way, we achieved the synthesis of [$^{15}N_2$]adenosines and [$^{15}N_2$]-2′-deoxyadenosines[4d] and of [$^{15}N_2$]guanosines.[4e]

In this context, we planned to compare the reactivity of dihalo derivatives of 9-(2′,3′,5′-tri-*O*-acetylribofuranosyl)purines **1–3** among them and against different kinds of amides. Differences were expected,[1] but we found out suitable conditions for the selective replacement of one halogen or the other, including those for the replacement of I at 0 °C, which we report here for the first time.



1, X = Cl
2, X = Br
3, X = I

Purine nucleosides, owing to their sensitivity to Lewis and Brönsted acids, which may give rise to the cleavage of the anomeric bonds and removal of the protecting groups (PGs), and to bases—with the removal of some PGs as well—are ideal substrates for testing the performance of a catalytic system; mild reaction conditions and short reaction times are a must, otherwise decomposition products predominate. In sharp contrast to what happens in many cross-coupling reactions, the substrates are often[4e] much more expensive than the Pd and P reagents. In the present work we have used nucleosides with Ac groups as PGs, as they were the most convenient during the synthesis of the starting materials. As it is also known, unlike S_NAr-like reactions, where the order of substitution of aryl halides by a nucleophilic nitrogen is usually F > Cl > Br > I,[5] in Pd-catalysed reactions the opposite order is observed, I > Br ≫ Cl >>> F,[1] since the insertion of Pd^0 into the C–X bond is generally the rate-determining step. Moreover, in 2,6-dichloro derivative **1**, position 6 is the most reactive (both in Pd-catalysed and S_NAr/S_NHet processes).[4e,5] In the case of 6-chloro-2-iodo-9-isopropylpurine, Piguel and Legraverend showed that the Pd-catalysed reaction takes place at the C2 position with

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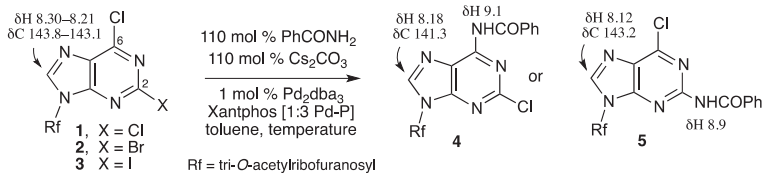
Table 1
Pd^0-catalysed reactions of 2,6-dihalopurine nucleosides with benzamide, at different temperatures[a]



Entry	Compound	*T* (°C)	Time	Conv. (%)	Product, yield[b] (%)
1	**1**	20	48 h	0	—
2	**1**	50	6 h	15	**4**, 10
3	**1**	80	6 h	100	**4**, 87
4	**2**	20	48 h	40	**5**, 35
5	**2**	50	3 h	100	**5**, 86
6	**2**	80	1 h	100	**5**, 80[c]
7	**3**	20	24 h	100	**5**, 88
8	**3**	50	2 h	100	**5**, 87
9	**3**	80	40 min	100	**5**, 82[c]

[a] Reaction conditions: 0.1 M in anhyd. toluene, under Ar, 1.0 mol % of $Pd_2dba_3{\cdot}CHCl_3$ (that is, 0.02 equiv of Pd^0), 3.0 mol % of Xantphos. Some experiments repeated with Pd_2dba_3 and $Pd(dba)_2$ (2 mol % in this last case) did not show significant differences.[12]
[b] Isolated yields after flash column chromatography.
[c] The dibenzamido derivative was detected (5–10%). See the main text.

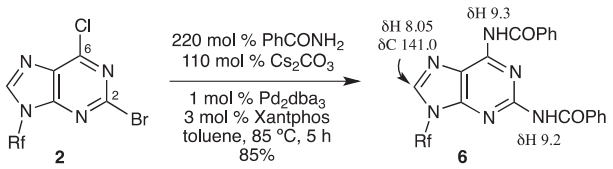
full regioselectivity,[6] that is, the preference of Pd^0 to insert into the C2–I bond overcomes the higher intrinsic reactivity of position 6 in S_NHet reactions. In this connection, 2-bromo-6-chloro derivative **2** is a more challenging case, that is, a very appropriate substrate for the evaluation of the relative significance of both effects.

Thus, we treated **1–3**[7] with benzamide as a representative nitrogen source, in the presence of 1 mol % of $Pd_2dba_3{\cdot}CHCl_3$ (dba = dibenzylideneacetone = 1,5-diphenyl-1,4-pentadien-3-one) and 3 mol % of Xantphos [4,5-bis(diphenylphosphino)-9,9-dimethylxanthene],[8] at different temperatures, as shown in Table 1. Although we had the feeling that the amount of catalyst could be even lower, we were more interested in avoiding long reaction times (owing to the possible decomposition of the nucleosidic substrates, as mentioned).

With 2,6-dichloro derivative **1**, a temperature of 80 °C was required for its total conversion to **4** (Table 1, compare entries 1–3).[9] Substitution only took place on C6 (the product of substitution at C2, see **5**, was not detected, under these conditions).

With **2** and **3**, the replacements of Br and I at C2, respectively, were complete at 50 °C (Table 1, entries 5 and 8) to give **5**.[10] The mass spectra of the products, showing in one case the replacement of 2-Br (but not that of 6-Cl) and in the other one the replacement of 2-I (but not that of 6-Cl), were conclusive. The reactivity differences between **2** and **3** were, however, significant at 20 °C (compare entries 4 to 7). To summarize, the reactivity order appeared to be 2-I > 2-Br > 6-Cl ≫ 2-Cl. The order 2-I > 2-Br > 2-Cl was expected, but the 'position' of 6-Cl in this scale was unknown.

The case of **2** (2-Br vs 6-Cl) was the more interesting one. Below 80 °C we only observed the replacement of 2-Br (**5**, entry 5). At 80 °C, we detected a minor disubstitution product (footnote to entry 6 of Table 1, see **6** below). Regarding the amount of base, the same outcome was obtained with 60 mol % as with 110 mol % of Cs_2CO_3; therefore, in these heterocyclic systems an excess of base is not crucial (saving of base is possible). Moreover, without Pd/Xantphos but with an excess of Cs_2CO_3, the reactions were very slow since, after 24 h at 80 °C in toluene, <10% of substitution at C6 took place. Even at 100 °C for 24 h with 2 equiv $PhCONH_2$ and 200 mol % of Cs_2CO_3, in the presence of Xantphos (but without Pd, of course), the substitution percentages were low (around 10%). Thus, the disubstitution byproduct—the observation of substitution at C6 in the experiments at 80 °C for ⩽1 h, indicated in



Scheme 1. Pd^0-catalysed double substitution of **2** with benzamide.

entries 6 and 9 of Table 1—does not come from a S_NAr-like mechanism.

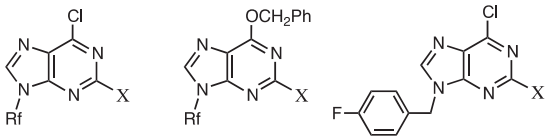
We then repeated the reaction of **2** with twice the amount of $PhCONH_2$, at 85 °C, with only 1 mol % of $Pd_2dba_3{\cdot}CHCl_3$, 3 mol % of Xantphos and 110 mol % of Cs_2CO_3, as indicated in Scheme 1. Compound **2** was fully converted into 2,6-dibenzamido derivative **6**.[11] The isolated yield was 85%.

Therefore, it appears that the Pd^0 insertion occurs selectively at the more reactive C2–Br bond, but once this bromine atom has been replaced to a large extent, the insertion of Pd^0 into the C6–Cl bond becomes competitive when the reaction temperature is ⩾80 °C.

As the reaction of **3** had been complete at rt (Table 1, entry 7), we examined such a reaction at 0 °C. In toluene, the formation of the active Pd–Xantphos species[13] (that is, the dba-to-Xantphos exchange) was not observed and benzamide was quite insoluble, so that the reaction did not go forward. However, it was sufficient to warm Pd_2dba_3 and Xantphos in toluene (at 60 °C for a few seconds) and, after cooling to 0 °C, to add a solution of **3** and benzamide in a similar volume of 1,4-dioxane to note a smooth progress of the cross-coupling reaction, as shown in entry 1 of Table 2, with no secondary reactions (no deacetylation byproducts were observed at all). To the best of our knowledge (exhaustive SciFinder search), there are no precedents of efficient Pd-catalysed amidations carried out below room temperature.[14] The replacement of the iodine atom of **3** was selective under these conditions as the bromo derivative, **2**, did not react at all.

Could other similarly activated iodine atoms be selectively replaced below rt? We examined the Pd-catalysed reaction of $PhCONH_2$ with two additional substrates (**7** and **8**, Table 2).[15] Good

Table 2
Pd^0-catalysed reactions of iodo derivatives **3**, **7** and **8** with benzamide at 0 °C[a]



3, X = I
5, X = NHCOPh

7, X = I
9, X = NHCOPh

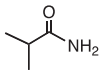
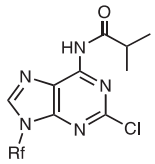
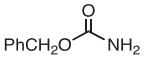
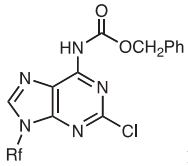
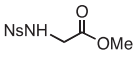
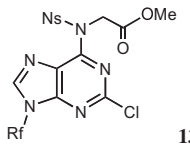
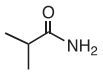
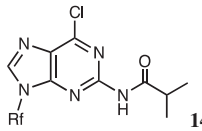
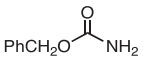
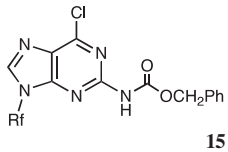
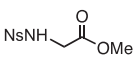
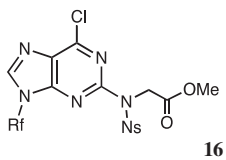
8, X = I
10, X = NHCOPh

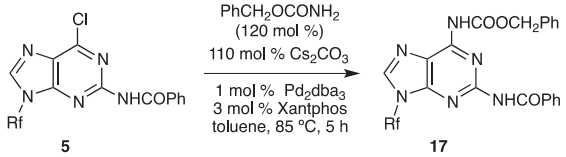
Entry	Iodo deriv., concn.	Pd_2dba_3, mol %	Time	Conv. (%)	Product, yield (%)
1	**3**, 0.1 M	1	48 h	100	**5**, 93
2	**3**, 0.2 M	1	24 h	100	**5**, 96
3	**7**, 0.2 M	1	36 h	100	**9**, 95
4	**8**, 0.1 M	2.5	48 h[b]	100	**10**, 94[b]
5	**8**, 0.2 M	2.5	28 h	100	**10**, 95

[a] $Pd_2dba_3{\cdot}CHCl_3$ (0.040 mmol) and Xantphos (0.120 mmol) in anhyd. toluene (10 mL) were warmed under Ar. As soon as the wine-red suspension became greenish yellow (formation of the Pd–Xantphos complex),[13] the flask was cooled to 0 °C (stock solution stored under Ar). For entries 2, 3 and 5, an aliquot (2.5 mL) was added via syringe to a vial (bath at 0 °C) with anhyd. Cs_2CO_3 (1.1 mmol). Afterwards, the iodo derivative (1.0 mmol) and benzamide (1.2 mmol) in 1,4-dioxane (2.5 mL), where benzamide is soluble, was added via syringe, and stirring was maintained at 0 °C for the time indicated, always under Ar.

[b] This experiment was repeated using a 1:2.1 Pd/P ratio instead of the standard 1:3 ratio, with a practically identical efficiency (conversion/time).

Table 3
Pd^0-catalysed reactions of **1** and **2** with amides, carbamates or nosylamides at 80 °C for 6 h, with the reagent ratios of Table 1

Entry	Compd.	Nucleoph.	Product	Yield %
1	**1**		 **11**	85
2	**1**		 **12**	77
3	**1**		 **13**	87
4	**2**		 **14**	82
5	**2**		 **15**	78
6	**2**		 **16**	84



Scheme 2. Preparation of a N^2,N^6-disubstituted 2,6-diaminopurine.

conversions were observed, although the reactions were slightly slower than in the case of **3**. To shorten the reaction times, we enhanced the substrate concentration to 0.2 M (see entries 2, 3 and 5) and/or that of the catalyst (entries 4 and 5); of course, there is room for improvement by operating at higher concentrations and with a large excess of $PhCONH_2$, but we did not examine it. On the other hand, as it could be expected, iodobenzene did not react at all under these so mild conditions. In other words, only the most reactive C–I bonds undergo the insertion of the Pd^0/Xantphos complex below rt.

Finally, to evaluate the scope of the reaction, other N-nucleophiles were subjected to the standard conditions (Table 3). We chose **1** and **2** (instead of **3**) as substrates because they are more challenging instances, never reported before, where the substitutions at C2 and C6 can compete. Isobutyramide, *O*-benzyl carbamate,[16] and *N*-2-nitrobenzenesulfonylglycine methyl ester (*o*-nosyl-$NHCH_2COOMe$, Ns-Gly-OMe) were chosen as nucleophile models. Although there are precedents of Pd-catalysed N-arylations of sulfonamides,[17] we have not found examples with the less reactive *o*-nosylamides;[18] the Ns protecting group is more readily removed than standard sulfonyl groups.[19] Reactions ran parallel to those of benzamide and isobutyramide, although they were slower.[20]

Replacement of halo substituents by two different amides, carbamates or sulfonamides seemed possible and could be an entry to diverse conjugates of 2,6-diamino-purines. As an example or 'proof of concept' we treated **5** with benzyl carbamate and Cs_2CO_3 in the presence of Pd^0/Xantphos (Scheme 2), in toluene at 85 °C for 5 h, which gave disubstituted product **17**. The conversion was complete but a partial decomposition of the carbamate group was noted (the isolated yield was around 60%).[21]

Only the activation of the 2-Cl substituent of **1** (and of **11–13**) remained a challenge. We had attempted this replacement by forcing the reaction conditions in refluxing 1,4-dioxane but the crude contained many decomposition products. However, the conversion of **1** into the dibenzamido derivative, **6**, could be achieved in toluene at 108–110 °C (bath temperature), in 90% isolated yield, within 6 h, with 2.5 mol % of $Pd_2(dba)_3$, 7.5 mol % of Xantphos and 110 mol % of Cs_2CO_3.

In summary, Pd^0 and Xantphos are very suitable partners for the coupling of halopurine nucleosides with amides (either carboxamides, carbamates or nosylamides). The regioselectivity–reactivity order is 2-I > 2-Br > 6-Cl ≫ 2-Cl (the 2-I > 2-Br > 2-Cl order was expected, but the point was to establish the 'position' of 6-Cl). We have achieved the replacement of the iodine atom of 6-iodo-2-chloro derivative **3** (and other similar iodo derivatives) at 0 °C, a temperature at which the bromine of **2** is not substituted at all. Such a reactivity order permits to manipulate 2,6-dihalopurines in a proper way to attach protected amine groups either at C2 or C6. Via Pd-catalysed processes, it is also feasible to prepare differently N^2,N^6-disubstituted diaminopurines (potential nucleoside conjugates). Finally, even the more reluctant 2-Cl substituent can be replaced by a benzamido group, in toluene at 110 °C, with a minimum amount of Cs_2CO_3 and reaction times as short as possible to avoid byproducts coming from the decomposition or saponification of sensitive substrates (protected purine nucleosides).

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5. There are exceptions, however, depending on the nucleophile and medium. For an update, see: (a) Liu, J.; Robins, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 5962–5968, and references cited therein; (b) we have confirmed in our lab that, with a commercially available solution of NH_3 in 1,4-dioxane (0.5 M), it was easy to introduce an amino group at C6, either at 50 °C (overnight) or 80 °C (for 2 h) from **1–3** in a closed vial, without affecting at all bromine and iodine atoms at C2, that is, the reactions were very clean and, in spite of using 5 equiv of NH_3, no substitution at C2 was observed; the chlorine atom of 6-chloro-2-cyano and 6-chloro-2-(benzylamino)carbonyl derivatives had been replaced by us under identical conditions (see: Bosch, L.; Vilarrasa, J. *Tetrahedron Lett.* **2011**, *52*, 753–756); (c) in our hands, ammonia in anhydrous dioxane does not cleave the ester groups of the monosaccharide ring (see Robins, M. J.; Uznanski, B. *Can. J. Chem.* **1981**, *59*, 2608–2611, for related observations in DME); the amino-dechlorination reactions were almost quantitative.
6. (a) Piguel, S.; Legraverend, M. *J. Org. Chem.* **2007**, *72*, 7026–7029; also see: (b) Vandromme, L.; Legraverend, M.; Kreimerman, S.; Lozach, O.; Meijer, L.; Grierson, D. S. *Bioorg. Med. Chem.* **2007**, *15*, 130–141; (c) Li, X.; Vince, R. *Bioorg. Med. Chem* **2006**, *14*, 5742–5755; (d) Ibrahim, N.; Legraverend, M. *J. Comb. Chem* **2009**, *11*, 658–666; for other Pd-catalysed aminations and amidations of purines and purine nucleosides see Ref. 1.
7. Dichloro derivative **1** was prepared according to Refs.[4e,5] as well as from the 2-amino-6-chloropurine nucleoside by diazotisation and halo-dediazoniation (*tert*-butyl nitrite or isopentyl nitrite, Me_3SiCl, CH_2Cl_2); see: (a) Francom, P.; Robins, M. J. *J. Org. Chem.* **2003**, *68*, 666–669; 2-bromo-6-chloro derivative **2** was also obtained by the last procedure (with Me_3SiBr and CH_2Br_2 instead). We prepared 6-chloro-2-iodo derivative **3** by a related procedure, viz., by treatment of the amine with isopentyl nitrite, I_2, CH_2I_2 and CuI in THF; see: (b) Matsuda, A.; Shinozaki, M.; Yamaguchi, T.; Homma, H.; Nomoto, R.; Miyasaka, T.; Watanabe, Y.; Abiru, T. *J. Med. Chem.* **1992**, *35*, 241–252; (c) Nair, V.; Richardson, S. G. *Synthesis* **1982**, 670–672.
8. For a review, see: Birkholz, M.-N.; Freixa, Z.; van Leeuwen, P. W. N. M. *Chem. Soc. Rev.* **2009**, *38*, 1099–1118.
9. 6-Benzamido-2-chloro-9-(2′,3′,5′-tri-O-acetyl-β-D-ribofuranosyl)-purine (**4**): white foam; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.07 (s, 3H), 2.12 (s, 3H), 2.15 (s, 3H), 4.39 (d, J = 3.6 Hz, 2H), 4.45 (m, 1H), 5.58 (dd, J = 4.1, 5.5, 1H), 5.80 (t, J = 5.7, 1H), 6.24 (d, J = 5.9, 1H), 7.49 (t, J = 7.7, 2H), 7.59 (t, J = 7.4, 1H), 8.00 (d, J = 7.3, 2H), 8.18 (s, 1H), 9.09 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 20.3 (CH_3), 20.5 (CH_3), 20.7 (CH_3), 63.0 (CH_2), 70.6 (CH), 73.1 (CH), 80.6 (CH), 85.8 (CH), 122.8 (C), 128.0 (CH), 128.8 (CH), 132.6 (C), 133.1 (CH), 141.3 (CH), 150.6 (C), 153.6 (C), 153.8 (C), 164.4 (C), 169.3 (C), 169.5 (C), 170.2 (C); HRMS (ESI) m/z calcd for $[C_{23}H_{23}{}^{35}ClN_5O_8]^+$ (M+H$^+$) 532.1235 and $[C_{23}H_{22}{}^{35}ClN_5NaO_8]^+$ (M+Na$^+$) 554.1055, found 532.1228 and 554.1046.
10. 2-Benzamido-6-chloro-9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)purine (**5**): white solid foam; mp 70–71 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.07 (s, 3H), 2.11 (s, 3H), 2.17 (s, 3H), 4.53 (m, 3H), 5.95 (m, 2H), 6.16 (d, J = 3.9, 1H), 7.50 (t, J = 7.5, 2H), 7.58 (t, J = 7.4, 1H), 7.96 (d, J = 7.2, 2H), 8.14 (s, 1H), 8.91 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 20.4 (CH_3), 20.5 (CH_3), 20.7 (CH_3), 63.5 (CH_2), 70.8 (CH), 73.6 (CH), 80.6 (CH), 87.5 (CH), 127.5 (CH), 128.8 (CH), 129.0 (C), 132.5 (CH), 133.9 (C), 143.2 (CH), 151.6 (C), 152.0 (C), 152.2 (C), 164.1 (C), 169.5 (C), 169.5 (C), 169.6 (C); HRMS (ESI) m/z calcd for $[C_{23}H_{23}{}^{35}ClN_5O_8]^+$ (M+H$^+$) 532.1235 and $[C_{23}H_{22}{}^{35}ClN_5NaO_8]^+$ (M+Na$^+$) 554.1055, found 532.1239 and 554.1060.
11. 2,6-Dibenzamido-9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)purine (**6**): white solid foam; mp 109–110 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.06 (s, 3H), 2.10 (s, 3H), 2.15 (s, 3H), 4.50 (m, 3H), 5.99 (m, 2H), 6.16 (d, J = 2.5, 1H), 7.48 (m, 4H), 7.54 (m, 2H), 8.00 (m, 4H), 8.05 (s, 1H), 9.21 (br s, 1H), 9.34 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 20.4 (CH_3), 20.5 (CH_3), 20.7 (CH_3), 63.4 (CH_2), 70.8 (CH), 73.4 (CH), 80.3 (CH), 86.9 (CH), 120.7 (C), 127.6 (CH), 127.9 (CH), 128.6 (CH), 128.7 (CH), 132.1 (CH), 132.7 (CH), 133.2 (C), 134.2 (C), 141.0 (CH), 150.1 (C), 152.5 (C), 152.6 (C), 164.7 (C), 164.7 (C), 169.5 (C), 169.6 (C), 170.4 (C); HRMS (ESI) m/z calcd for $[C_{30}H_{29}N_6O_9]^+$ (M+H$^+$) 617.1996 and $[C_{30}H_{28}N_6NaO_9]^+$, (M+Na$^+$) 639.1815, found 617.1992 and 639.1822.
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