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2-CYANO Δ^3 PIPERIDEINE VII [1] THE CONDENSATION OF 2-CYANO Δ^3 PIPERIDEINE WITH SODIUM DIMETHYLMALONATE CATALYZED BY $ZnCl_2$ OR ZERO VALENT PALLADIUM AND PLATINUM COMPLEXES

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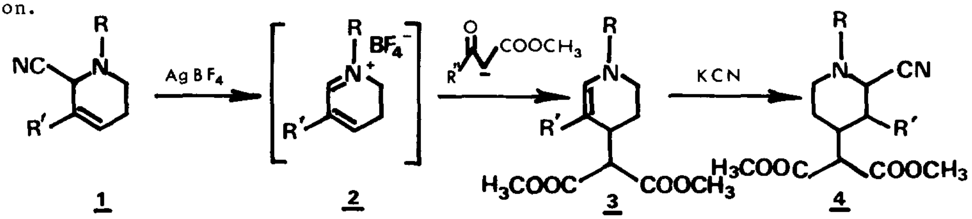
Abstract $ZnCl_2$, Pd $(P\phi_3)_4$ and $Pt(P\phi_3)_4$ were found to be effective catalysts for the condensation of sodium dimethyl malonate with 2-cyano Δ^3 piperideine 1 a-d

The key step in a number of projects in progress in our laboratory[b] directed towards the synthesis of alkaloids [2] involves the condensation of a 2-cyano Δ^3 piperideine with a 1,3-dicarbonyl anion which leads to the regiospecific formation of the C-4 substituted enamine 3, or when desired, to the aminonitrile 4 (by treatment of 3, with aqueous KCN) (scheme 1, for R" = OCH_3). We have found that highly reproducible results are obtained in this reaction when the leaving group capacity of the cyano group is enhanced through its complexation with Ag^+ ion ($AgBF_4$)[3] Mechanistically an elimination-addition process is felt to occur wherein the dihydropyridinium salt 2 generated progressively from a silver(I) complex of 1 reacts in a conjugate or Michael fashion with the stabilized enolate anion.



Scheme 1

The necessary use of stoichiometric amounts of Ag^+ to complex 1 becomes an undesirable feature of this reaction, however, when conducting experiments on a large scale (>25 mmol) In an effort to circumvent this problem we have directed our attention towards examining reagents which might effect the transformation $1 \rightarrow 3$ catalytically. We have now found that the condensation of sodium dimethylmalonate with the aminonitriles 1a-d may be efficiently performed using catalytic amounts of anhydrous $ZnCl_2$ or catalytic amounts of the zero valent organometallic complexes Pd $(P\phi_3)_4$ and Pt $(P\phi_3)_4$. A summary of our results and experimental procedure is presented in Table 1

The choice of $ZnCl_2$ as catalyst was made in the anticipation that Zn^{2+} would not be precipitated like Ag^+ from the reaction medium on reaction with aminonitriles 1a-d It was found that a reasonable rate of condensation could be achieved using a 10 mol % proportion of this reagent. The reaction of dimethylmalonate anion with aminonitriles 1a-d in the presence of $ZnCl_2$ also led uniquely to the formation of the enamines 3a-d [4] In this instance however reintroduction of the cyano group to give products 4a-d directly was prevented due to the insolubility of the NaCN produced in the reaction medium [3].

TABLE 1 EXPERIMENTAL RESULTS

1	Catalyst [a,d]	°C	Time hrs	% 4 [6,e]
a R = CH_3	A	60°	24	72
R' = H	B	"	"	70
	C	"	8	75
b R = CH_3	A	60°	48	89 [b]
R' = C_2H_5	B	"	"	80 [b]
	C	"	16	76
c R = $CH_2C_6H_5$	A	60°	24	75
R' = H	C		16	77
d R = $CH_2C_6H_5$	A	60°	48	(70)[b,c]
R'= C_2H_5	C	"	"	67[b]

a) A = 5% $Pd(P\emptyset_3)_4$, B = 5% Pt $(P\emptyset_3)_4$, C = 10% $ZnCl_2$

b) Compound 4 was isolated as an $\sim$8 2 mixture of isomers.

c) reaction incomplete, % yield determined by integration of the ^1H NMR spectrum.

d) 1 (1 mmol), sodium dimethylmalonate (1 5-1.7 mmol), catalyst, $\emptyset_3P$(30mg) (for catalysts A and B only) reacted in THF (8ml) at 60° under an atmosphere of argon.

e) purified by column chromatography on alumina (1 x 12cm) eluting with CH_2Cl_2 hexane-mixture

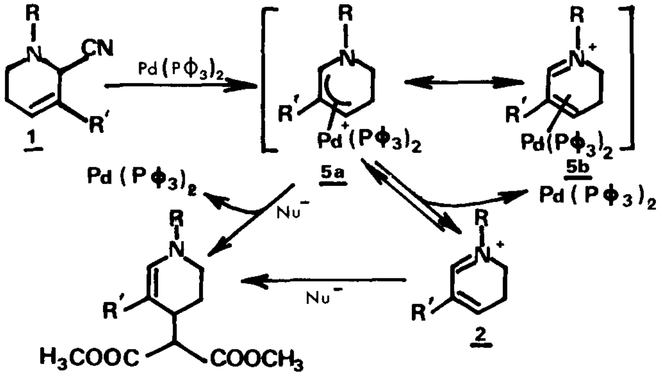
Although longer reaction times and higher temperatures were required for complete reaction than were necessary using stoichiometric amounts of $AgBF_4$ (15-60 min.) no significant change in the yields of the isolated products 4a-d[5] was observed In fact the crude products obtained from these reactions were found to the remarkably free of contaminants. The analogous product mixtures obtained from the Ag^+ promoted reactions were contamined with unidentified highly coloured polar materials which rendered purification more difficult.

It was not unexpected that a long reaction time (48 hrs) would be necessary for the preparation of compound 4d from the hindered substrate 1d (compared with results for 2d). The lower yield (67%) obtained in this case may simply reflect the sensitivity of enamine 3d to prolonged heating in the presence of the acidic catalyst[6]

Zero valent Pd and Pt complexes were studied as catalysts based upon the recognition that the 2-cyano Δ^3 piperideine molecule contains an allylic moiety wherein the CN reacts as a leaving groups through participation of the lone pair of electrons on nitrogen. This system thus a priori contains the essential features necessary for the formation of a π-allyl metal complex The subsequent reaction of such complexes with malonate anions is well documented[7].

Indeed an efficient condensation reaction was observed when 5 mol % of Pd $(P\emptyset_3)_4$ was added to the mixture of 1 and dimethylmalonate anion[8]. Reaction times[9] ranged between 24-48 hrs at 60° depending upon the substrate (except for the hindered substrate 1d where reaction did not go to completion before catalyst activity was lost) Again NaCN precipitated from the reaction medium and the C-4 substituted enamines 3a-d were produced in essentially pure form On isolation of the corresponding aminonitriles 4a-c the yields were found to be comparable with those obtained using $ZnCl_2$

In keeping with the generally accepted mechanism for Pd° (and Pt°) catalyzed alkylation reactions [7d,10] the first step in the condensation probably involves reaction of amino nitrile 1 with Pd $(P\phi_3)_2$ resulting in elimination of CN and formation of a π-allyl palladium complex 5a (for which the iminium species 5b may be a contributing mesomeric form) (scheme 2). This complex may then react either directly with sodium dimethylmalonate giving 3 or undergo prior elimination of Pd $(P\phi_3)_2$ to give the dihydropyridinium salt 2 followed by conjugate addition of malonate anion



Scheme 2

At present we do not have definite proof for the formation of the π-allyl complex 5, or for the mechanism of its electrophilic reaction. However, ^1H NMR evidence has been accumulated which shows that on reaction of 1b with Pd° a new entity is formed which exhibits a spectrum different than that observed for the dihydropyridinium salt 2 [3] It was at least clear from this study that the Pd° and Lewis acid catalyzed reaction did not follow the same initial course.

In conclusion, it has been found that the desired sequence 1 → 3 can be performed in good yields using either $ZnCl_2$ or zero valent organometallic complexes as catalysts. Both these catalyst systems have the advantage over the use of Ag^+ salts in that the reactions are cleaner The use of $ZnCl_2$ also provides a distinct economic advantage over the use of $AgBF_4$ when conducting large scale experiments

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4 A typical enamine absorption, 1640-1650cm^{-1}, was observed in the IR spectra of products 3a-d, and characteristic resonances were observed in the ^1H NMR spectra for the substited and unsubstituted systems.

5. The yields for the catalyzed reactions of 1a-d with dimethyl malonate anion were calculated for the aminonitriles 4a-d and not for the initial reaction products 3a-d since they were less sensitive to purification by column chromatography.

4a (colourless solid) ^{1}H NMR ($CDCl_3$) δ 2.38 (s, 3H, NCH_3), 3.28 (d, J = 9Hz, 1H, CH), 3.75 (s, 6H, OCH_3), 3.87 (m, 1H, H-2) , ^{13}C NMR ($CDCl_3$) δ 29.0, 31.9, 32.3, 43.8, 50.3, 52.6 (2), 54.5, 56.4, 115.8, 168.5 (2) , MS m/e (rel. intensity) 254 (100% $M^{+\cdot}$), 253 (60%), 227 (20%), 223 (50%).

4b. (colourless oil), an ∿ 8 2 mixture of two isomers , Major isomer ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, J = 6Hz, 3H, CH_3), 2.37 (s, 3H, NCH_3), 3.63 (d, J = 3Hz, 1H, CH), 3.68, 3.72 (2s, 6H, OCH_3, both isomers), 3.89 (d, J = 3Hz, 1H, H-2) , ^{13}C NMR ($CDCl_3$) δ 10.8, 22.0, 27.4, 37.8, 42.0, 44.0, 50.6, 51.6, 58.8, 114.5, (52.3(4), 168(4)), (Minor isomer ^{1}H NMR ($CDCl_3$) 0.86 (t, J = 6Hz, CH_3), 2.31 (s, NCH_3), 3.78 (br.S, H-2) , ^{13}C NMR δ 12.2, 17.4, 24.8, 35.6, 40.8, 50.4, 54.5, 56.8

4c (colourless oil) , ^{1}H NMR ($CDCl_3$) δ 3.26 (d, J = 9Hz, 1H, CH), 3.61 (m, 2H, $CH_2\phi$) 3.74, 3.76 (2s, 6H, OCH_3), 3.83 (m, 1H, H-2) , ^{13}C NMR ($CDCl_3$) δ 29.0, 32.1, 32.6, 48.9, 51.6, 52.4 (2), 56.3, 60.1, 115.9, 127.6, 128.6, 128.9, 136.8, 168.1 (2) , MS m/e (rel. intensity) 330 (60%, M^{+}), 329 (100%), 299 (20%), 271 (10%), 252 (30%), 239 (70%), 172 (80%).

4d (colourless oil) an ∿ 8 2 mixture of isomers , Major isomer ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (t, J = 6Hz, 3H, CH_3), 3.67 (AB quartet, J = 12Hz, 2H, $CH_2\phi$), 3.70 (d, J = 4Hz, 1H, CH), 3.75 (s, 6H, OCH_3), 3.90 (d, J = 3Hz, 1H, H-2) , ^{13}C NMR ($CDCl_3$) δ 10.8 22.2, 27.4, 38.6, 42.0, 49.0, 51.8, 52.5 (2), 56.4, 60.4, 115.2, 169.0 (2) , Minor Isomer ^{13}C NMR ($CDCl_3$) 11.0, 24.1, 25.3, 35.4, 40.8, 46.4, 52.8 (2), 118.0, 169.0 (2)

6. Endocyclic piperidine enamines are well known to be relatively fragile entities, see : S.J. Martinez, J.A Joule, Tetrahedron, 1978, 34, 3027.

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8. To our knowledge this is the first example of a palladium catalyzed allylation reaction in which CN has behaved as a leaving group. In a related system, α,β-unsaturated cyanohydrin acetate, allylation occured with loss of OAC^- and not CN^-, see J. Tsuji, H. Ueno, Y. Kobayashi, H Okumoto, Tetrahedron Letters, 1981, 22, 2573.

9. No increase in the reaction rate was observed when Pd $(P\phi_3)_4$ was replaced by $Pd(P(O\phi_3)_4$ Pd $(diphos)_2$ or Pd $(P\phi_3)_4/ZnCl_2$, see B M. Trost, N R Schmuff, M J Miller, J Am. Chem. Soc , 1980, 102, 5891 , J Godschax, J K. Stille, Tetrahedron Letters, 1980, 21, 2599 When DMF was used as the solvent rather than THF a partial isomerization of 1 to the corresponding 2-cyano Δ^2 piperidine was observed (see ref. 3).

10 See however a) J.C Fiaud, J L Malleron, Tetrahedron Letters, 1981, 22, 1399 , b) B Akermark, G Akermard, L.S. Hegedus, K Zatterberg, J Am Chem Soc., 1981, 103, 3037, c) L S Hegedus, B Akermark, D J Olsen, O. P Anderson and K. Zetterberg, ibid, 1982, 104, 697

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