N^5N^{10}-Methenyltetrahydrofolate Models. One-carbon Unit Transfer *via* Imidazolidine Derivatives

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Summary Suitably substituted imidazolidinium salts serve as N^5N^{10}-methenyltetrahydrofolate models in terms of their ability to transfer a formyl equivalent to a variety of mono- and bi-functional nucleophiles.

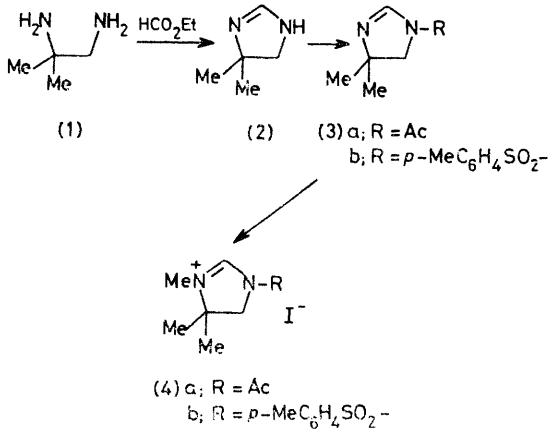
THE metabolic interconversions of tetrahydrofolate coenzymes involve the transfer of one-carbon units at different oxidation levels.[1] Owing to our interest in the development of synthetic methods based upon mechanisms of biochemical processes,[2] we have examined the utility of suitable imidazolidine derivatives as potential donors of a one-carbon fragment, at the formyl level. We here present results which illustrate the principle of the C_1-unit transfer process, in terms of the reaction of the imidazolidinium salts (**4a**) and (**4b**) with a variety of nucleophiles. While in many reactions the isolated product represents a net one-carbon transfer, in others the intermediate prior to this overall process has been obtained (Table).

TABLE. Products/intermediates of one-carbon unit transfer.

Reagent	Substrate		Isolated product	Yield/%
(**4a**)	PhMgBr	(**5**)	PhCHO[a]	45
(**4a**)	4-$MeOC_6H_4MgBr$	(**6**)	4-$MeOC_6H_4CHO$[a]	70
(**4a**)	4-ClC_6H_4MgBr	(**7**)	4-ClC_6H_4CHO[a]	90
(**4b**)	$PhNH_2$	(**8**)	$Ph{=}CH{-}N^+Me$–A I^-	90
(**4b**)	$PhCH_2NH_2$	(**9**)	$PhCH_2NH{-}CH{=}N^+Me$–A I^-	81
(**4b**)	$Et_2NCOCH_2NH_2$	(**10**)	Et_2NCOCH_2NMe–A[b]	80
(**4b**)	$CH_2(CO_2Et)_2$	(**11**)	$(EtO_2C)_2C{=}CH{-}N{=}CH{-}NMe$–A	65
(**4b**)	$Ph_3P^+C^-HCO_2Et$	(**12**)	$EtO_2CC^-(P^+Ph_3)CH{=}N^+Me$–A I^-	85
(**4b**)	2-$HOC_6H_4NH_2$	(**13**)	2-HOC_6H_4NHCHO[a]	32
(**4b**)	2-$H_2NC_6H_4NH_2$	(**14**)	Benzimidazole	52
(**4b**)	2-$H_2NC_6H_4SH$	(**15**)	Benzthiazole	80
(**4b**)	5,6-Diaminopyrimidine	(**16**)	Purine	17
(**4b**)	H_2N-$[CH_2]_n$-NH_2 n = 3, 4, 5, 6, or 9	(**17**)	$HN{-}CH{=}N^+H[CH_2]_n$ I^-	80—100

A = $-CMe_2CH_2NHO_2SC_6H_4Me$-*p*. [a] Upon hydrolysis. [b] Upon treatment with Et_3N.

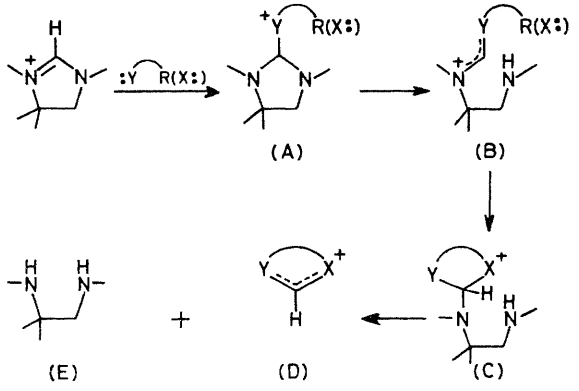
The imidazolidinium salts (**4a,b**) (Scheme 1), which correspond to models of the N^5N^{10}-methenyltetrahydrofolate system, can be conveniently prepared as follows. Commercially available (Aldrich) diamine (**1**) is converted into the imidazolidine (**2**), by reaction with ethyl formate (48%). Acetylation or tosylation of (**2**) gives (**3a**) (70%)



SCHEME 1

or (**3b**) (100%), respectively, which, when treated with methyl iodide afford the salts (**4a,b**) as crystalline products: (**4a**) m.p. 231—236 °C, 80%; (**4b**) m.p. 184—186 °C, 78%. Although, on steric grounds, it was expected that acetylation or tosylation of (**2**) would occur at the nitrogen atom remote from the *gem*-dimethyl group, the structure of (**4b**) was established by identification of its hydrolytic product, namely, $OCHN(Me)CMe_2CH_2NHO_2SC_6H_4Me$-*p*. Particularly revealing was the n.m.r. spectrum of this *N*-formyl compound which exhibited coupling of the methylene group with the proton on the nitrogen ($-CH_2NHO_2SC_6H_4Me$-*p*).

The reactions of the imidazolidinium salts (**4a,b**) with diverse nucleophiles (**5**)—(**17**) (Table) were carried out under conditions which were determined by the reactivity of the substrates in question: (a) Grignard reagents (**5**)—(**7**), tetrahydrofuran (THF), room temp., hydrolysis with $(CO_2H)_2$–H_2O; (b) monoamines (**8**)—(**10**), MeCN, room temp.; (c) bifunctional nucleophiles (**13**)—(**17**), MeCN, reflux, 16 h; (d) diethyl malonate (**11**), NaH–THF, room temp.; and (e) the ylide (**12**), MeCN, room temp. The mechanism of formation of all products described in the Table can be rationalized by the processes outlined in Scheme 2. The



SCHEME 2

initial product of attack of monofunctional nucleophiles (:Y⌒R) is the aminal (A), which in the case of reaction with the Grignard reagents, has been isolated and identified. The aminal (A) constitutes the precursor of the corresponding aldehydes. If the nucleophile carries an acidic hydrogen, a proton transfer to one of the ring-nitrogens occurs; subsequent ring-opening of the imidazolidine system forms the thermodynamically favoured salt (A → B). The latter transformation leads to stable products in the reactions of (**4b**) with the monofunctional amines (**8**)—(**10**), diethyl malonate anion (**11** + NaH), and the ylide (**12**). With bifunctional nucleophiles, (:Y⌒X:), the intermediate corresponding to (B) undergoes nucleophilic attack by the group X: at the iminium carbon, to result in a second intermediate (C). This readily decomposes to the product of an overall one-carbon unit transfer process (D) and the diamine (E). (D) is isolated as a salt in the reaction with the diamines (**17**), (n = 3—6, or 9) or as a neutral product in the case of the aromatic bifunctional nucleophiles (**14**)—(**16**). The isolation of 2-formamidophenol upon

work-up of the reaction with (**13**) is consistent with the known ease of hydrolysis of the expected benzoxazole, which presumably is the primary product. The products of the reaction of (**4b**) with the malonate anion (**11**), the ylide (**12**), and the diamines (**17**) are potentially useful synthons in their own right. The utility of these as well as the scope of C_1-unit transfer from tetrahydrofolate models will be discussed in detail elsewhere.

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[1] S. J. Benkovic and W. P. Bullard in 'Progress in Bio-organic Chemistry,' vol. 2, eds. E. T. Kaiser and F. J. Kézdy, Wiley-Interscience, New York, 1973, p. 133.

[2] The utility of NADH-models in several types of reduction processes has been reported. See *e.g.*: U. K. Pandit, M. J. de Nie-Sarink, A. M. v. d. Burg, J. B. Steevens, and R. F. M. van Dokkum, *Rec. Trav. chim.*, 1978, **97**, 149; U. K. Pandit, R. A. Gase, F. R. Mas Cabré, and V. den Breejen-Metz, *ibid.*, 1977, **96**, 215; U. K. Pandit, H. van Dam, and J. B. Steevens, *Tetrahedron Letters*, 1977, 913; and R. A. Gase and U. K. Pandit, *J.C.S. Chem. Comm.*, 1977, 480.