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BASE-CATALYSED CYCLISATION OF N-ALKYL-(E)-STILBENE-2-CARBOXAMIDES

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Abstract: When the N-substituent is a not-hindered alkyl group, the title compounds (1) cyclise to the corresponding N-alkyl-3-benzylphthalimidines (2).

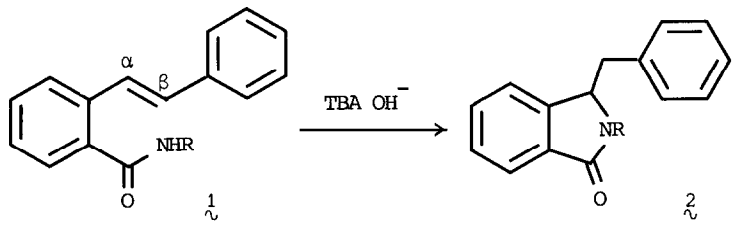
Our interest in the preparation of N-substituted 3-benzylphthalimidines (2), which may also constitute important intermediates in our new synthesis of isoquinoline alkaloids of the proto_berberine series,[1] led us to investigate the possibility of obtaining these compounds by induc_ing a direct cyclisation in appropriate N-substituted (E)-stilbene-2-carboxamides (1). Although the reaction had some precedent,[2] the differences in the substitution pattern around the double bond in (1) with respect to the model compound (in particular, the lack of a chlorine atom at position β) did not permit to predict a straightforward extension of the reaction to our case.

We have now found that some N-alkyl-(E)-stilbene-2-carboxamides (1), when stirred overnight in a two-phase system (CH_2Cl_2-33% $NaOH_{aq}$) in the presence of tetrabutylammonium (TBA) hydrogen sulphate, undergo cyclisation to N-alkyl-3-benzylphthalimidines (2) in high yields (a case of 5-Exo-Trig ring closure).[3] The alternative mode of cyclisation to the N-alkyl-3,4-dihydroisocar_bostiryls (6-Endo-Trig ring closure) did not apparently take place in these conditions. Thus, compounds 1a, 1b, and 1c gave compounds 2a, 2b, and 2c, respectively. The reaction does not apply to the parent amide 1d, which gave an intractable mixture, and to the hindered amide 1e, which was recovered unreacted even after a longer reaction time. A unique behaviour was exhibit_ed by the anilide 1f, which apparently underwent isomerisation around the amide bond.[4]

The structures of compounds 2a and 2b have been unambiguously deduced by comparison with samples obtained by reaction of 3-benzylidenephthalide with the proper alkylamine, dehydration of the adduct and catalytic hydrogenation of the N-alkyl-3-benzylidenephthalimidine.[5]

Although the latter sequence has been so far the most obvious method of preparation of com_pounds of general formula 2, the novel cyclisation may turn out to be the method of choice in the case of molecules containing acid sensitive groups (e.g. 2c), or groups sensitive to cata_

lytic hydrogenation. Work is in progress to test whether this reaction can be employed to prepare intermediates useful in the synthesis of alkaloids and alkaloid analogues of the rhoeadine series.



1

1a R=CH_3; 1b R=CH_2Ph; 1c R=$CH_2CH(OCH_3)_2$; 1d R=H; 1e R=$C(CH_3)_3$; 1f R=Ph
2a R=CH_3; 2b R=CH_2Ph; 2c R=$CH_2CH(OCH_3)_2$

Physical and spectral data of compounds.[8] 1a: mp 149-151°C; ν(nujol) 3300 (NH), 1630 (CO) cm^{-1}; δ($CDCl_3$) 2.87 (d, J=5.0 Hz, 3, CH_3), 6.18 (b. s, 1, NH), 7.00-7.82 (m, 11, aromatic and vinylic). 1b: mp 124-126°C; ν(nujol) 3300 (NH), 1630 (CO) cm^{-1}; δ($CDCl_3$) 4.48 (d, J=7.0 Hz, 2, CH_2), 6.50 (b. s, 1, NH), 7.00-7.57 (m, 16, aromatic and vinylic). 1c: mp 90-93°C; ν(nujol) 3300 (NH), 1620 (CO) cm^{-1}; δ($CDCl_3$) 3.35 (s, 6, OCH_3), 3.62 (t, J=5.0 Hz, 2, CH_2), 4.50 (t, J=5.0 Hz, 1, $CHCH_2$), 6.12 (b. s, 1, NH), 7.15-7.82 (m, 11, aromatic and vinylic). 1d: mp 190-191°C (lit.[6] mp 191-192°C). 1e: mp 123-125°C; ν(nujol) 3270 (NH), 1630 (CO) cm^{-1}; δ($CDCl_3$) 1.45 (s, 12, CH_3), 5.71 (b. s, 1, NH), 7.12-7.77 (m, 11, aromatic and vinylic). 1f: mp 171-172°C. 2a: oil; ν(neat) 1680 (CO) cm^{-1}; δ ($CDCl_3$) 2.68, 2.82, 2.92, 3.03, 3.21, 3.30, 3.45, 3.53 (ABXm, 2, CH_2CH), 3.13 (s, 3, CH_3), 4.57, 4.75, 4.69, 4.77 (ABXm, 1, CH_2CH), 6.88-9.91 (m, 9, aromatic). 2b: mp 83-84°C (lit.[7] mp 83-85°C). 2c: oil, ν(neat) 1680 (CO) cm^{-1}; δ($CDCl_3$) 3.42, 3.47 (two s, 3+3, OCH_3), 2.52-3.68 and 4.13-5.13 (two superimposed ABX systems, 6, other aliphatic protons), 6.85-7.92 (m, 9, aromatic).

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References and footnotes.

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2. G. Berti, Gazz. Chim. Ital., 90, 559 (1960).
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4. This argument will be treated in more detail in a forthcoming paper.
5. See, e.g., U.S.P. 2 957 872 (1960); C.A., 55, 16489b (1961).
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8. All compounds gave satisfactory elemental analyses.

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