New Short Syntheses of Isoquinoline-4-carboxylic Acid and 2-Aza-3,3a-dihydroazulene-3a-carboxylic Acid Derivatives

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Cyclopropylideneacetates (**2a,b**) undergo a formal [2 + 4] cycloaddition with (diphenylmethylene)amine (DPMA-H) (**1**) to yield dihydro-1-phenylisoquinoline-4-carboxylate (**8a**) and 1-phenylisoquinoline-4-carboxylate (**7b**); the Michael adduct of DPMA-H onto (**2b**), on the other hand, under basic conditions gives 1-phenyl-2-aza-azulene-3a-carboxylate (**12**) exclusively.

Many isoquinoline alkaloids including several non-naturally occurring phenylisoquinolines have been noted for their physiological activity.[1] 1-Phenylisoquinoline-4-carboxylic acid amides like (**11**) have recently been reported as antiarrythmic drugs.[2] Other physiological activities have been observed for related compounds.[3] New synthetic routes to such compounds are of interest expecially if they lead to a substitution pattern which is difficult or impossible to obtain by classical methods.[4]

As was recently published, (diphenylmethylene)amine (DPMA-H, benzophenone imine) (**1**) reacts with methyl 2-chloro-2-cyclopropylideneacetate (**2b**),[5] a highly reactive Michael acceptor[6] and dienophile,[7,8] in dichloromethane with a catalytic amount of tertiary base or in alcohol to give the 1,4-adduct (**4b**) almost quantitatively within one day. In contrast, (**2b**) in dichloromethane containing sodium hydride‡ reacts with (**1**) much more slowly and gives the isoquinoline (**7b**) in 26% isolated yield (50% according to NMR), accompanied by an equal amount of (**4b**) (40% isolated).§ The yield was improved to 39% in neat tetrachloromethane (53% by NMR). The structure of (**7b**) was secured by spectroscopy, including COSY and COLOC (correlation by long range coupling) NMR techniques, and finally by *X*-ray crystallography.¶

The formation of (**7b**) is likely to proceed *via* the formal [4 + 2] cycloadduct (**5b**), which may be formed in either a concerted or a two-step tandem Michael reaction *via* the dipolar intermediate (**3b**).[9] Intermediate (**5b**) would immediately be transformed to the dihydroisoquinoline (**8b**).[10] This is confirmed by the analogous reaction of (**1**) with methyl cyclopropylideneacetate (**2a**)[11] which gives methyl spiro-[cyclopropane-1,3′(3a′*H*)-(1′-phenylisoquinoline-4-carboxylate)] (**8a**) in 32% isolated yield (58% by NMR).[9]¶ The facile aromatization of (**8b**) with its cyclopropylmethyl chloride moiety is to be expected considering the lability of comparable systems, *e.g.*, of spiro[2.5]octadiene derivatives with good leaving groups.[12]

Michael adduct (**4b**) is thermally stable in refluxing CCl_4. Thus (**7b**) is not formed from (**4b**) *via* ring-opening of the cyclopropylmethyl chloride to a homoallyl chloride unit[12] followed by a 6π-electrocyclic ring-closure[15] with final oxidative aromatization. An oxidative cyclization of (**4**) to give (**8**) is also unlikely since solutions of (**4a,b**) are stable to air and even to Ce^{IV}[14] or Cu^{II}. As Diels–Alder reactions are often promoted by cation radical initiators,[15] the addition of catalytic amounts of tris(4-bromophenyl)aminium hexachloroantimonate to the mixture of (**1**) and (**2b**) was tested, but had no effect on the reaction.

When the esterenolate (**6b**) was generated from (**4b**) with lithium di-isopropylamide (LDA) or potassium t-butoxide no products derived from (**5b**) were found. Instead, the carbenoid (**6b**) forms methyl spiro[cyclopropane-1,3′(3a′*H*)-(1′-phenyl-2′-aza-azulene-3a′-carboxylate)] (**12**) by an astonishingly efficient addition of the carbene to one of the phenyl groups (47 and 70% yield, respectively).§¶ It is noteworthy that the intermediate cyclopropylcarbene does not undergo the usually facile rearrangement to the corresponding cyclobutene.[16]

The observed isoquinoline formation from (**1**) and (**2**) may be one of the rare examples of a [2 + 4] cycloaddition with a 1-azadiene.[17] In spite of the fair yields this synthesis is competitive with known routes to comparable compounds as

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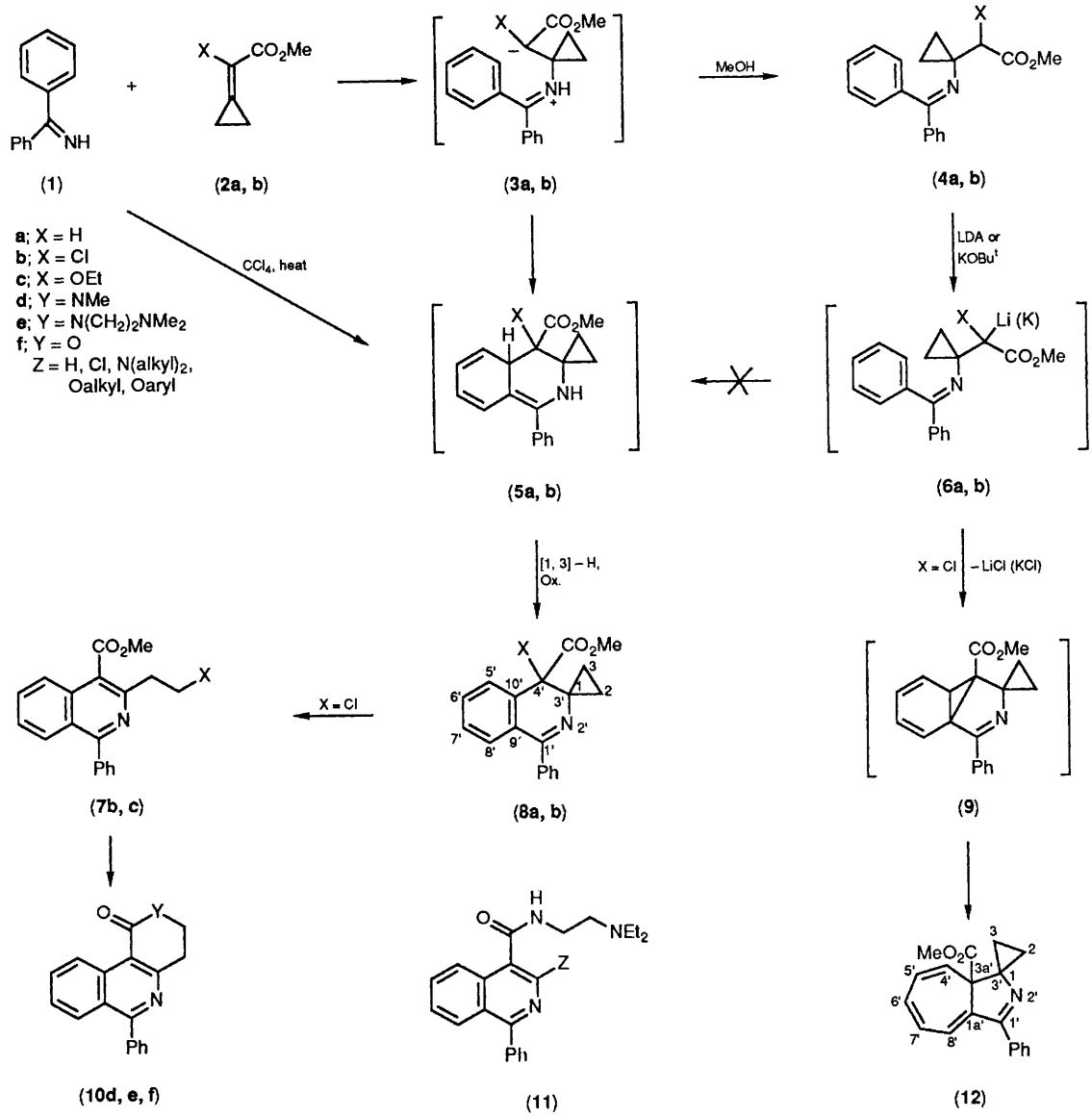
‡ We are uncertain about the effect of sodium hydride; in the absence of it (**7b**) is also formed, but in poorer yield.

§ All new compounds gave satisfactory microanalytical and spectroscopic data.

¶ *Spectroscopic data* for (**7b**), (**8a**), and (**12**). (**7b**): m.p. (uncorrected): 83 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.49 (t, ^3J 7.7 Hz, 2H, CH_2-aryl), 4.07 (t, ^3J 7.7 Hz, 2H, CH_2Cl), 4.12 (s, 3H, OMe), 7.51—7.60 (m, 4H, *m,p*-$H_{arom.}$, 7-H), 7.67—7.77 (m, 3H, *o*-$H_{arom.}$, 6-H), 7.96 (dd, ^3J 8.5 Hz, 1H, 5-H), 8.11 (dd, ^3J 8.5 Hz, 1H, 8-H); ^{13}C NMR (100.63 MHz, $CDCl_3$) δ 39.27 (CH_2-Aryl), 43.32 (CH_2Cl), 52.58 (OMe), 123.27 (C-4), 127.46 (C-5), 125.06 (C-9), 127.22 (C-7), 127.90 (C-8), 128.39 (2C, *m*-$C_{arom.}$), 129.05 (*p*-$C_{arom.}$), 130.00 (2C, *o*-$C_{arom.}$), 131.09 (C-6), 134.30 (C-10), 138.92 (i-$C_{arom.}$), 148.11 (C-3), 162.08 (C-1), 168.66 (CO_2Me); IR (KBr) ν 2960 (C–H), 1721 (C=O), 1250, 1210, 1053, 702 cm^{-1}; MS (70 eV): *m/z* (%) 327 (2.4), 325 (6.8, M^+), 291 (23), 290 (100, M − Cl), 230 (11).

(**8a**): m.p. (uncorrected): 112 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (mc, 1H, 2-H), 1.02 (mc, 1H, 2-H), 1.38 (mc, 1H, 3-H), 1.50 (mc, 1H, 3-H), 3.28 (s, 1H, 4′-H), 3.63 (s, 3H, OMe), 7.25—7.34 (m, 3H, *m,p*-$H_{arom.}$) 7.38—7.46 (m, 4H, 6′-H, 7′-H, *o*-$H_{arom.}$), 7.55—7.60 (m, 2H, 5′-H, 8′-H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.75 (C-3), 16.65 (C-2), 40.65 (C-1), 49.25 (C-4′), 52.03 (OMe), 127.82 [C-7′, C-8′ (uncertain assignment)], 128.06 [C-5′, *m*-$C_{arom.}$ (uncertain assignment)], 128.39 (*o*-$C_{arom.}$), 128.58 (C-9′), 128.90 (*p*-$C_{arom.}$), 130.86 (C-6′), 133.27 (C-10′), 138.27 (*i*-$C_{arom.}$), 167.17 (C-1′), 171.74 (CO_2Me); IR (KBr) ν 2990, 2940 (C–H), 1725 (C=O), 1320, 1235, 700 cm^{-1}, CI MS (Bu^i): *m/z* (%) 292 (100%, MH^+), 232 (30%, M −CO_2Me). mc = centrosymmetric multiplet.

(**12**): m.p. (uncorrected): 109 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.17 (mc, 2H, cyclopropyl-H), 1.59 (mc, 2H, cyclopropyl-H), 3.50 (s, 3H, OMe), 5.47 (d, ^3J 9.8 Hz, 1H, 4′-H), 6.42 (mc, 1H, 5′-H), 6.63 (mc, 2H, 6′-H, 7′-H), 6.79 (mc, 1H, 8′-H), 7.40—7.45 (m, 3H, *m,p*-$H_{arom.}$), 7.58—7.44 (m, 2H, *o*-$H_{arom.}$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 15.06 (cyclopropyl-CH_2), 15.09 (cyclopropyl-CH_2), 51.81 (OMe), 57.13 (C-3a′), 63.55 (C-1), 121.76 (C-8′), 122.74 (C-4′), 126.22 (C-5′), 128.18 (2C, *o*-$C_{arom.}$), 128.30 (2C, *m*-$C_{arom.}$), 128.92 (C-7′), 129.56 (*p*-$C_{arom.}$), 131.25 (C-6′), 133.48 (i-$C_{arom.}$), 139.19 (C-8a′), 168.09 (C-1′), 171.48 (CO_2Me); IR (KBr) ν 1745 (C=O), 1255, 1220, 775, 708 cm^{-1}; MS (70 eV): *m/z* (%) 291 (3.7, M^+), 232 (100, M − CO_2Me), 178 (8.2).



for example (**11**). || Further transformations on the ester group in (**12**), (**8a**), and (**7b**) as well as the 2-chloroethyl group in (**7b**) are easily achieved. Thus (**7b**) gives the ethoxyethyl derivative (**7c**) with ethanol, methylamine and 2-dimethylaminoethylamine give the lactames (**10d**) (93%) and (**10e**) (92%), respectively. Reaction of the free acid derived from (**10c**) with thionyl chloride yields the lactone (**10f**) (96%).§

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|| Crude (**11**) (Z = H) had been synthesized in 6 steps with ~27% overall yield, involving strongly acidic, oxidative and reductive conditions[4a] [(**10e**) 2 steps, 36% overall yield]. The comparable Pomeranz–Fritsch reaction usually is not applicable to 1-phenylisoquinolines,[4c] whereas the Pictet–Gams method gives *e.g.*, 3-ethyl-1-phenylisoquinoline in 26% yield only[4b] and yet without the pharmacologically important carboxy substituent.

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