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A Free Radical Route to the Benzazepines and Dibenzazepines

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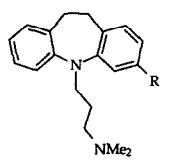
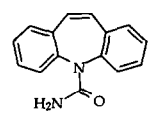
Abstract Free radical ring expansion of six membered azocycles provides a new entry to the preparation of benzazepines and dibenzazepines.

Benzazepines and dibenzazepines have important pharmacological activity. Dibenzazepines include imipramine and clomipramine, substances widely used for the treatment of depressive illness.[1,2,3] The 5H-dibenz[b,f]azepine-5-carboxamide (carbamazepine) is a well known



Imipramine, R=H
Clomipramine, R=Cl



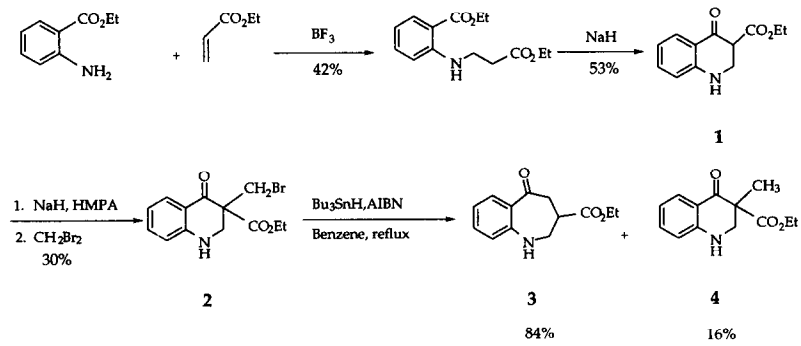
Carbamazepine

analgesic and anticonvulsant. In this paper, we report the free radical ring expansion of six-membered azocycles leading to the synthesis of benzazepines and dibenzazepines by a novel route. The intermediate seven-membered benzazepine γ-keto ester in this synthesis may also be of value in the synthesis of alkaloids and other products with biologically useful properties.

For the benzazepines, preparation of the required β-keto ester **1** makes use of a Dieckmann condensation of the Michael adduct of ethyl anthranilate with ethyl acrylate[4] (Scheme 1). Alkylation of **1** with dibromomethane and sodium hydride in refluxing

tetrahydrofuran yielded the adduct **2** (Scheme 1). Tri-*n*-butyltin hydride was added to a refluxing

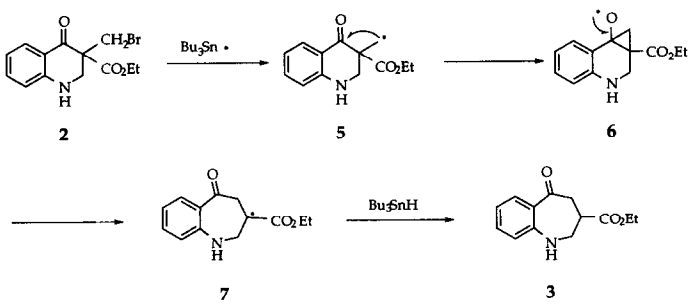
Scheme 1



benzene solution of **2** using a syringe pump over a 10 h period with a catalytic amount of AIBN. The ring expansion product **3** [5] was obtained (84%) with a minor amount of the direct reduction product **4** (16%).

Following earlier examples of free radical ring expansion[6], it is reasonable to suggest that formation of the primary radical **5** is followed by attack on the ketone (Scheme 2). The resulting

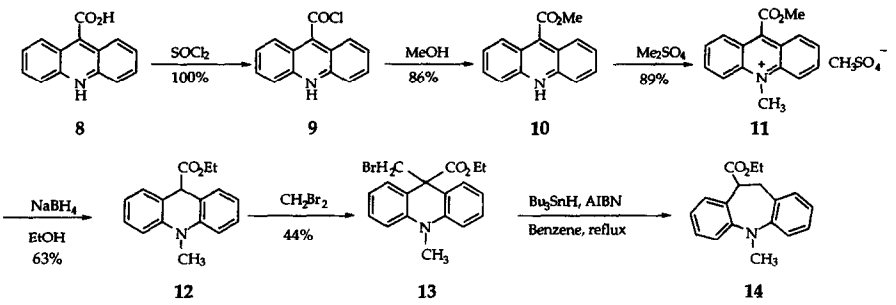
Scheme 2



alkoxyl radical then undergoes regiospecific ring-opening leading to the ester-stablized radical **7**.

For the dibenzazepines, the starting 9-acridinecarboxylic acid **8** was converted to its ester according to a literature procedure[3,7] (Scheme 3). Thus, treatment of **8** with thionyl chloride yielded the acid chloride **9** (100%) which was then converted to the corresponding methyl ester **10** by methanolysis (86%). Methylation of **10** with dimethyl sulfate yielded the quaternary amine salt **11** (89%), which was then reduced to **12** with sodium borohydride (63%).

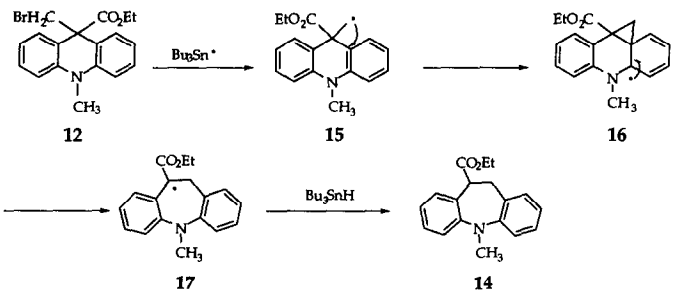
Scheme 3



Alkylation of **12** with dibromomethane and sodium hydride in tetrahydrofuran at room temperature for 16 h yielded **13**, which was treated in refluxing benzene with AIBN and Bu_3SnH (syringe pump, 10 h) and led smoothly to the ring expansion product **14** (68%).[8]

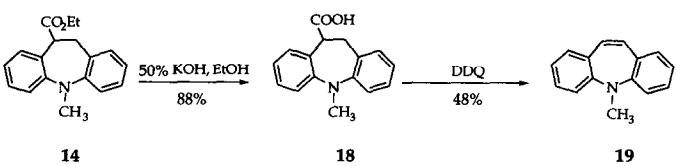
Rearrangement of the primary radical **15** is assisted by the formation of the conjugated radical **16**.[9] Opening of **16** leads to the more stable radical **17**, which can then abstract a hydrogen atom from Bu_3SnH to produce the desired product **14** (Scheme 4).

Scheme 4



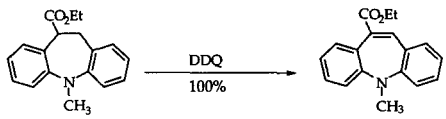
The ester group of **14** can be removed, eliminated or converted to other functional groups and a further series of dibenzazepines can be prepared. For example, after hydrolysis of ethyl ester **14**, the resulting acid **18** was decarboxylated to the corresponding N-methyldibenzazepines **19** (Scheme 5) by treatment with DDQ.

Scheme 5



DDQ was also used to dehydrogenate **14** to **20** (Scheme 6), maintaining the skeleton of the

Scheme 6



14 **20**

dibenzazepine with the additional ester available for transformation to other functional groups.

Since the substituent on nitrogen can readily be varied, the free radical route provides a general, clean, high-yield route to the synthesis of benzazepines and dibenzazepines.

Acknowledgement

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5. Compound **3** : ^{1}H-NMR-$CDCl_3$ (ppm): 7.70 (d, 1H), 7.25 (t, 1H), 6.85 (t, 1H), 6.70 (d, 1H), 4.65 (s, 1H), 4.2 (q, 2H), 3.85 (m, 1H), 3.25 (m, 3H), 2.95 (m, 1H), 1.25 (t, 3H). ^{13}C-NMR-$CDCl_3$ (ppm): 200.2, 193.0, 153.3, 132.8, 129.6, 124.9, 119.1, 117.6, 61.3, 50.1, 47.8, 43.0, 14.2. IR (KBr,cm^{-1}): 3352.7 (vs, N-H), 1728.4 (vs, C=O), 1645.5 (vs, C=O). MS (m/e): 233 (M^+, 50), 188 (20), 160 (30), 133 (100), 105 (40). mp 64-65.0 °C.
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8. Compound **10:** ^{1}H-NMR-$CDCl_3$ (ppm) 7.39-6.31 (m, ArH, 8H), 4.14 (m, 3H), 3.43(q, 1H), 3.36 (m, 1H), 3.34 (s, 3H), 1.19 (t, 3H). ^{13}CNMR-$CDCl_3$ (ppm): 173.6, 148.7, 148.1, 131.7, 130.3, 129.8, 129.2, 127.7, 126.8, 122.6, 122.0, 119.6, 118.3, 60.7, 47.9, 39.7, 34.7, 14.3. IR (KBr, cm^{-1}): 1728.4 (vs, C=O). MS (m/e): 281 (40), 208 (100), 193 (60), 179 (10), 65 (10). m.p. 62-62.5 °C.
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