

## A Retro-malonate Addition Reaction: Synthesis of 3,4-Condensed Heteroaromatic Pyrroles

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Treatment of bromo alkylidenemalonates (1)—(4) with ammonia or amines afforded 3,4-condensed heteroaromatic pyrroles (5)—(8) in excellent yields; benzotripyrroles (19)—(21) were synthesized by the same method.

3,4-Condensed heteroaromatic pyrroles are synthetically<sup>1</sup> and theoretically<sup>2</sup> interesting. Current interest in the preparation of organic conducting polymers based on heteroaromatic monomers<sup>3</sup> has stimulated a search for new practical syntheses of heteroaromatic pyrroles.<sup>4</sup> In continuation of our previous work,<sup>5</sup> we report here a new expeditious synthesis of 3,4-condensed heteroaromatic pyrroles by a novel retro-malonate addition reaction.<sup>6</sup>

Treatment of the bromoalkylidenemalonates (1),<sup>5</sup> (2),<sup>7</sup> (3),<sup>†</sup> and (4)<sup>‡</sup> with ammonia or amines in ethanol afforded the heteroaromatic pyrroles (5),<sup>10</sup> (6),<sup>11</sup> (7),<sup>12</sup> and (8)<sup>§</sup> in one step

† Compound (3) was prepared by the method in ref. 5, from 3-methylpyrazine-2-carbaldehyde, made in turn from 2,3-dimethylpyrazine by first bromination (*N*-bromosuccinimide) and subsequent oxidation with the sodium salt of 2-nitropropane.<sup>8</sup>

‡ Compound (4) was prepared by the method in ref. 5 from 3-methylbenzofuran-2-carbaldehyde, made in turn from ethyl 3-methylbenzofuran-2-carboxylate<sup>9</sup> by reduction (LiAlH<sub>4</sub>) and subsequent oxidation with Me<sub>2</sub>SO, (COCl)<sub>2</sub>, and Et<sub>3</sub>N (Swern oxidation).

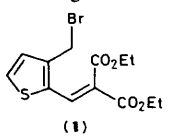
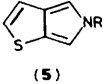
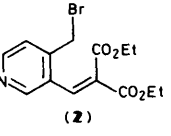
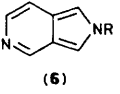
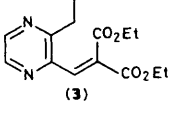
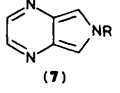
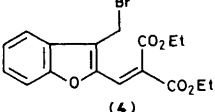
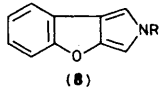
§ <sup>1</sup>H N.m.r. data for compound (8a) (400 MHz; CDCl<sub>3</sub>): δ 7.63 (dd, 1 H, *J* 7.28 and 1.04 Hz), 7.40 (d, 1 H, *J* 7.68 Hz), 7.22 (m, 2 H), 6.72 (d, 1 H, *J* 1.30 Hz), 6.49 (d, 1 H, *J* 1.30 Hz), and 3.77 (s, 3 H).

(see Table 1). Although the ring systems (5)—(7) have been synthesized by other methods, the benzofuro[2,3-*c*]pyrrole ring system (8) was synthesized for the first time.

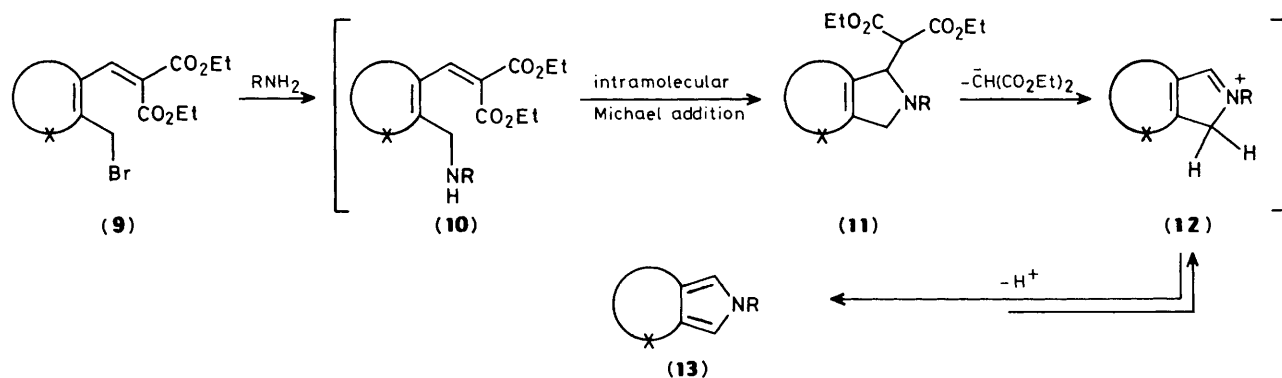
We rationalize the transformation by the mechanism shown in Scheme 1. The first step is the S<sub>N</sub>2 reaction of the amine with the benzylic bromide moiety in (9) to give the amino alkylidenemalonate (10). When aniline or *t*-butylamine was used as nucleophile the reaction could be followed by n.m.r. spectroscopy and the intermediate (10) could be isolated before the mixture was heated to reflux. The intermediate (10) subsequently undergoes intramolecular Michael addition to give the intermediate (11). Finally, retro-malonate addition occurs with elimination of diethyl malonate anion, to give (12), which then loses a proton to give the heteroaromatic pyrrole (13).

The reaction was carried out by stirring a solution of bromo alkylidenemalonate (1)—(4) and an excess of amine (3—10 equiv.) in ethanol at room temperature and then under reflux for 1—48 h (Table 1). Evaporation, followed by silica gel flash column chromatography, gave the products (5)—(8). Reactions of *t*-butylamine or aniline with the bromo alkylidenemalonates (1)—(4) required higher temperatures (70—80 °C) and longer reaction times; other amines reacted at room tempera-

**Table 1.** Preparation of 3,4-condensed heteroaromatic pyrroles (5)–(8).

Starting materials	Conditions <sup>a</sup>	Products <sup>b</sup>	Yields (%) <sup>c</sup>
	NH <sub>3</sub> (10 equiv.), EtOH, r.t. 30 min MeNH <sub>2</sub> (10 equiv.), EtOH, r.t. 1 h Pr <sup>i</sup> NH <sub>2</sub> (3 equiv.), EtOH, r.t. 1.5 h Bu <sup>t</sup> NH <sub>2</sub> (3 equiv.), EtOH, r.t. 1 h and reflux 5 h PhCH <sub>2</sub> NH <sub>2</sub> (3 equiv.), EtOH, r.t. 1 h PhNH <sub>2</sub> (3 equiv.), EtOH, r.t. 12 h and reflux 12 h		(5)a; R = H 30 b; R = Me 88 c; R = Pr <sup>i</sup> 86 d; R = Bu <sup>t</sup> 86 e; R = CH <sub>2</sub> Ph 78 f; R = Ph 60
	MeNH <sub>2</sub> (10 equiv.), EtOH, r.t. 3 h Pr <sup>i</sup> NH <sub>2</sub> (3 equiv.), EtOH, r.t. 3 h Bu <sup>t</sup> NH <sub>2</sub> (10 equiv.), EtOH, r.t. 2 h and reflux 3 h PhCH <sub>2</sub> NH <sub>2</sub> (3 equiv.), EtOH, r.t. 5 h PhNH <sub>2</sub> (3 equiv.), EtOH, r.t. 0.5 h and reflux 3 h		(6)a; R = Me 40 b; R = Pr <sup>i</sup> 89 c; R = Bu <sup>t</sup> 92 d; R = CH <sub>2</sub> Ph 90 e; R = Ph 74
	NH <sub>3</sub> (3 equiv.), EtOH, r.t. 12 h MeNH <sub>2</sub> (3 equiv.), EtOH, r.t. 2 h PhCH <sub>2</sub> NH <sub>2</sub> (3 equiv.), EtOH, r.t. 5 h and reflux 2 h PhNH <sub>2</sub> (3 equiv.), EtOH, reflux 3 h		(7)a; R = H 17 b; R = Me 67 c; R = CH <sub>2</sub> Ph 88 d; R = Ph 23
	MeNH <sub>2</sub> (10 equiv.), EtOH, r.t. 16 h Pr <sup>i</sup> NH <sub>2</sub> (3 equiv.), EtOH, r.t. 18 h PhCH <sub>2</sub> NH <sub>2</sub> (3 equiv.), EtOH, r.t. 22 h PhNH <sub>2</sub> (3 equiv.), EtOH, r.t. 24 h and 65 °C 20 h		(8)a; R = Me 59 b; R = Pr <sup>i</sup> 79 c; R = CH <sub>2</sub> Ph 80 d; R = Ph 20

<sup>a</sup> r.t. = room temperature. <sup>b</sup> All the products gave satisfactory n.m.r., i.r., and mass spectra. <sup>c</sup> Yields after silica gel flash column chromatography.

**Scheme 1**

ture and gave the products in higher yields. Reactions of ammonia with (1)–(4) all gave the crude parent ring systems of (5)–(8) (R = H) in good yield, but these parent compounds are highly labile and difficult to isolate. Upon silica gel flash column chromatography, only (5a) and (7a) could be isolated pure, in low yields (Table 1).

From mesitylene (14), we also prepared tribromo trialkylidenemalonate (18). Thus, reaction of (14) with paraformaldehyde and hydrobromic acid<sup>13</sup> gave the tribromide (15) (50%) (Scheme 2). Oxidation with the sodium salt of 2-nitropropane<sup>8</sup> then gave the trialdehyde (16) (98%). Knoevenagel condensation with diethyl malonate afforded the trialkylidenemalonate (17) (75%), and subsequent bromination with *N*-bromosuccinimide (NBS) and dibenzoyl peroxide gave (18) (75%). Reaction of (18) with benzylamine, *t*-butylamine, or aniline in *t*-butyl alcohol<sup>¶</sup> at room temperature gave

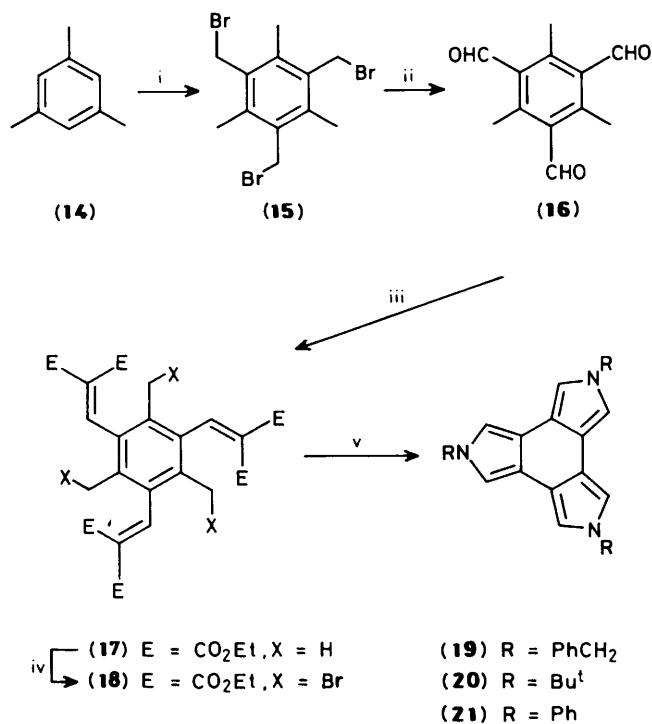
¶ Compound (18) reacted only slowly with ethanol; therefore *t*-butyl alcohol was used instead.

the benzotripyrrole (19)<sup>14</sup> (30%), (20) (8%), or (21) (47%), respectively.||

In conclusion, we report an expeditious and general method for the preparation of 3,4-condensed heteroaromatic pyrroles (5)–(8) and the benzotripyrroles (19)–(21). Although similar reactions of 2-(bromomethyl)arenealdehydes with amines could give the same products, we found in general that these aldehydes are not readily available.\*\* Bromoalkylidenemalonates, *e.g.* (1)–(4), thus serve as synthetic equivalents of 2-(bromomethyl)arenealdehydes.<sup>15</sup> The extension of this method to the synthesis of other heteroaromatic ring systems is under investigation.

|| The low yields of isolated (19)–(21) were due primarily to decomposition upon silica gel flash column chromatography.

\*\* For example, bromination of *o*-tolualdehyde with NBS only oxidized the aldehyde moiety to acid bromide.



**Scheme 2.** Reagents: i, (CH<sub>2</sub>O)<sub>n</sub>, HBr; ii, Pr<sup>i</sup>NO<sub>2</sub>Na; iii, CH<sub>2</sub>(CO<sub>2</sub>Et)<sub>2</sub>, TiCl<sub>4</sub>, pyridine; iv, NBS, dibenzoyl peroxide; v, benzylamine, t-butylamine, or aniline.

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