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A new improved method for the synthesis of 2,4-diarylpyrimidines starting from 2,2,2-trichloroethylideneacetophenones

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ABSTRACT

An advantageous new approach to 2,4-diarylpyrimidines has been developed. 2,2,2-Trichloroethylideneacetophenones reacted with benzamidines leading to novel 2,6-diaryl-6-hydroxy-4-trichloromethyl-1,4,5,6-tetrahydropyrimidines in near quantitative yields. These compounds were efficiently dehydrated to obtain previously unknown 2,4-diaryl-6-trichloromethyl-1,6-dihydropyrimidines, which were able to undergo aromatisation via chloroform elimination to give 2,4-diarylpyrimidines in high yields. A main improvement of this procedure lies in circumventing the oxidative dehydrogenation of dihydropyrimidine intermediates. This preparative process has also been adapted to a one-pot protocol.

The chemistry of pyrimidines has been extensively reviewed.[1–8] The development of preparative methods for these substances[1–6,8–22] has been strongly encouraged by a whole range of vital biological functions and important pharmacological activities.[23–26] Between the approaches to pyrimidines based on condensation processes, the method involving reactions between (+)C–C–C(+) dielectrophilic molecules and (−)N–C–N(−) dinucleophilic reagents, usually called 'common synthesis', is very popular.[7] Thus, the reaction between 1,3-dicarbonyl compounds and amidines provides an effective straightforward synthesis of pyrimidines.[27] Readily accessible α,β-unsaturated ketones have also been used as dielectrophiles to react with amidines. However, this is a less attractive option since the formation of pyrimidines requires oxidation of previously generated dihydropyrimidines instead of water elimination. Thus for example, reaction between equimolecular amounts of benzamidine and benzalacetophenone (chalcone) leads to 2,4,6-triphenylpyrimidine[9] in low yield (33%), which increases to 61% if an air stream is passed through the reaction mixture for a long time under basic and high temperature conditions. Nevertheless, if a similar reaction is carried out in the absence of oxygen, but with double the amount of chalcone, the formation of 2,4,6-triphenylpyrimidine reaches 85%, and is accompanied by benzylacetophenone (dihydrochalcone) (87%). This evidences that chalcone is able to oxidise the dihydropyrimidine intermediate involved to pyrimidine by undergoing reduction to dihydrochalcone. The main disadvantages of this alternative procedure are cost (double consumption of chalcone), practical difficulty (isolation of the targeted pyrimidine formed in mixture with dihydrochalcone) and a long reaction time. It should also be noted that Bignelli three-component reactions provide access to dihydropyrimidines, whose oxidative dehydrogenation has received much attention.[28] Alkynones[22,29] as well as enones possessing bromide and dimethylamino groups at the β-position[30–32] have also been reported as being usable to avoid the oxidation step.

Chloral is an inexpensive, multipurpose starting material for organic synthesis.[33] It is able to react with amides and acetophenones to yield primary intermediates from which we developed new synthetic methods for different classes of heterocyclic compounds via electrogeneration of chlorocarbanions by cathodic cleavage of carbon-chlorine bonds. On the basis of this reduction process we performed new preparative methods for several types of heterocyclic compounds.[34] Taking into consideration the successful results reported for the synthesis of sulfines, isocyanates and pyrimidinones, from trichloromethyl sulfoxides,[35] trichloroacetamides[36] and 4,4,4-trichloro-2-butenoic acid ethyl esters,[37] respectively, through unusual β-elimination of chloroform, we recognised the opportunity to improve the synthesis of pyrimidines and pyrimidine derivatives starting from easily available 2,2,2-trichloroethylideneacetophenones **3** and by exploring the behaviour of the trichloromethyl group as a good leaving group, instead of acting as a good electron transfer receptor. We previously reported[38] a detailed protocol for preparing compounds **3**. The key step of new pyrimidine synthetic route is a highly effective base catalysed β-elimination of chloroform, which allows the circumvention of any oxidative dehydrogenation step of dihydropyrimidine intermediates (Scheme 1). In addition, this approach shows another noteworthy advantage, since the synthesis can be carried

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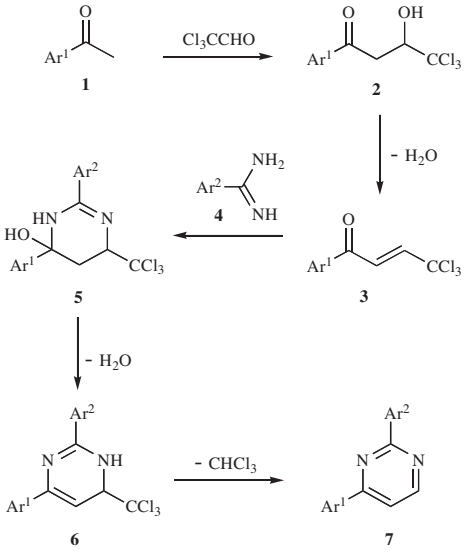

entry	Ar^1	Ar^2	5 (%)	6 (%)	7 (%)
a	4-$CH_3C_6H_4$	C_6H_5	89	78	79
b	4-ClC_6H_4	C_6H_5	93	78	82
c	4-BrC_6H_4	C_6H_5	90	73	90
d	4-$O_2NC_6H_4$	C_6H_5	93	68	77
e	4-$CH_3OC_6H_4$	3-$O_2NC_6H_4$	-	-	72
f	C_6H_5	3-$O_2NC_6H_4$	-	-	70
g	2-$C_{10}H_7$	4-$CH_3C_6H_4$	-	-	73

Scheme 1. Reaction sequence and yields in the formation of 2,4-diarylpyrimidines.

out either by following a stepwise procedure, making the isolation of new tetrahydro- and dihydropyrimidine compounds of potential biological interest feasible[28,39–41] or according to a one-pot protocol to directly yield the final pyrimidine products.

2,2,2-Trichloroethylideneacetophenones **3a–d** were prepared in high to near quantitative yields[38] by reaction of acetophenones **1** with chloral and subsequent dehydration of chloralacetophenones **2**. Compounds **3** reacted at room temperature with commercially available benzamidine until total conversion of starting materials to products[42] (clearly perceptible by TLC). Spectroscopic analyses revealed the generation of previously unknown 2,6-diaryl-6-hydroxy-4-trichloromethyl-1,4,5,6-tetrahydropyrimidines **5a–d**, which were isolated in high yields (89–93%) with a diastereomeric ratio of about 3:1. The major diasteromers were isolated by crystallisation. An X-ray crystallographic structural determination of **5b** showed a (4*RS*,6*RS*) configuration[43] for these diastereomers. Therefore, the configuration of the minor diasteromers was assigned to be (4*RS*,6*SR*).

Each diastereomeric pair of compounds **5a–d** was subjected to acidic dehydration under gentle heating[44] to give the corresponding dihydropyrimidines **6a–d** in fair to high yields (68–78%). These crystallised as single tautomers that were univocally identified as 2,4-diaryl-6-trichloromethyl-1,6-dihydropyrimidines by X-ray crystallography[43] of compound **6d**. Room temperature treatment of products **6a–d** with potassium *tert*-butoxide promoted a highly effective transformation providing single products that were identified as the targeted 2,4-diarylpyrimidines **7a–d**, whose formation clearly corresponds to an aromatisation process associated to a β-elimination of chloroform,[45] which was detected in the corresponding stoichiometric amount by capillary column gas chromatography. Yields were high (77–90%). After confirming the viability of this synthetic route, we successfully carried out a one-pot conversion of trichloroethylideneacetophenones **3e–g** to pyrimidines **7e–g** in good yields (70–73%) by reaction with commercial 3-nitrobenzamidine and 4-methylbenzamidine.[45] Compounds **7** were subjected to GC and HPLC analyses exhibiting single peaks. Geometrical characteristics of reaction products were determined by the X-ray crystallography[43] of product **7f**.

In summary, a novel and efficient synthetic method in pyrimidine chemistry is reported. The described protocol improves the interest and preparative potential of reactions between conjugated enones and benzamidines by circumventing any oxidative dehydrogenation process of dihydropyrimidine intermediates. This preparative strategy is operationally simple; the yields of the products are good; and the starting materials are readily available.

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Supplementary data

Supplementary data (^1H and ^{13}C NMR spectra of compounds **5**, **6** and **7**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.07.075.

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42. *Representative procedure for the preparation of products* ***5***: To a solution of **3** (1.0 mmol) in dry toluene (3 mL) a solution of **4** (1.2 mmol) in dry toluene (3 mL) was added dropwise. The reaction mixture was stirred for 2 h at room temperature. Then, the solvent was removed in vacuo and the solid residue was washed with cool hexane and crystallised from hexane/chloroform (**5b** mp 136–137 °C; **5c** mp 131–132 °C; **5d** mp 185–187 °C) or hexane (**5a**, mp 110–112 °C). The spectral data of product **5a** are reported as representative examples of spectroscopic properties of this class of substances: ^{1}H NMR δ (Acetonitrile-d_3, 200 MHz): 7.88–7.84 (m, 2H), 7.58–7.46 (m, 5H), 7.25 (d, 2H, J = 8.5 Hz), 6.83 (br s, 1H), 4.46 (dd, 1H, J = 12.0 Hz, J = 3.7 Hz), 4.42 (br s, 1H), 2.55 (dd, 1H, J = 12.7 Hz, J = 3.7 Hz), 2.38 (s, 3H), 1.76 (dd, 1H, J = 12.6 Hz, J = 12.0 Hz); ^{13}C NMR δ (Acetonitrile-d_3, 50.4 MHz): 155.01, 142.60, 138.97, 136.70, 131.33, 129.95, 129.26, 127.77, 126.68, 105.60, 81.28, 69.24, 38.94, 21.10; HRMS (ESI) m/z: calcd for $C_{18}H_{18}Cl_3N_2O$ $(M+H)^+$: 383.0479, found: 383.0475; IR (Nujol): 3420, 3280, 1613, 1575, 1505, 1470, 1377, 1310, 1230, 1133, 1105, 992, 900, 800, 789, 759, 701 cm^{-1}.
43. Details of the structure determination will be reported in a future full paper.
44. *Representative procedure for the preparation of products* ***6***: To a solution of **5** (1.0 mmol) in dichloromethane (15 mL) concentrated sulphuric acid (0.3 mmol) was added and the mixture was refluxed for 12 h. Then, the solvent was washed with aqueous sodium bicarbonate solution, dried over magnesium sulfate, and removed in vacuo, leaving a solid residue that was crystallised from petroleum ether/dichloromethane (**6a** mp 150–153 °C; **6b** mp 228–230 °C), petroleum ether (**6c** mp 231–234 °C) or toluene (**6d** mp 200–203 °C). The spectral data of product **6a** are reported as representative examples of spectroscopic properties of this class of substances: ^{1}H NMR δ ($CDCl_3$, 300 MHz): 7.81 (d, 2H, J = 8.1 Hz), 7.62 (d, 2H, J = 8.0 Hz), 7.42–7.36 (m, 3H), 7.14 (d, 2H, J = 7.9 Hz), 5.60 (d, 1H, J = 4.6 Hz), 4.88 (d, 1H, J = 4.8 Hz), 2.29 (s, 3H); ^{13}C NMR δ ($CDCl_3$, 75.4 MHz): 154.29, 154.27, 138.89, 134.44, 134.42, 131.32, 129.17, 128.77, 126.95, 125.70, 105.82, 95.53, 68.41, 21.27; HRMS (ESI) m/z: calcd for $C_{18}H_{16}Cl_3N_2$ $(M+H)^+$: 365.0374, found: 365.0368; IR (Nujol): 3420, 1621, 1592, 1565, 1514, 1484, 1463, 1377, 1356, 1316, 1250, 1113, 1016, 958, 808, 780, 766, 732, 714 cm^{-1}.
45. *Representative procedure for the preparation of products* ***7***: To a solution of **6** (1.0 mmol) in dry THF (25 mL) a 1.0 M solution of potassium *tert*-butoxide (1.0 mmol) in dry THF was added dropwise and the mixture was stirred for 4 h. After filtration the solvent was removed in vacuo, the solid residue was washed with a cool ethanol (3 mL) and crystallised from ethanol: **7a** mp 108–110 °C (Lit,[46] mp 109-110 °C); **7b** mp 88–90 °C; **7c** mp 106–108 °C (Lit,[47] mp 107–108 °C); *One-pot preparation:* Compounds **3** (1.0 mmol) were solved in acetonitrile (6 mL). After addition of the corresponding benzamidine **4** hydrochloride potassium carbonate (1.2 mmol) was added and the reaction mixture was refluxed under nitrogen atmosphere for 12 h. Then, the solvent was removed in vacuo, the residue was dissolved in chloroform (25 mL) that was washed with water (25 mL), dried over magnesium sulfate and removed in vacuo, leaving a residue that was crystallised from cyclohexane (**7f** mp 131–132 °C; **7g** mp 137–138 °C) or ethyl acetate (**7e** mp 170–171 °C). The spectral data of product **7a** are reported as representative examples of spectroscopic properties of this class of substances: ^{1}H NMR δ ($CDCl_3$, 300 MHz): 8.80 (d, 1H, J = 5.3 Hz), 8.61–8.57 (m, 2H), 8.14 (d, 2H, J = 8.2 Hz), 7.57–7.51 (m, 4H), 7.34 (d, 2H, J = 8.0 Hz), 2.45 (s, 3H); ^{13}C NMR δ ($CDCl_3$, 75.4 MHz): 164.43, 163.82, 157.59, 141.36, 137.89, 134.12, 130.62, 129.64, 128.48, 128.25, 127.09, 114.13, 21.45; HRMS (ESI) m/z: calcd for $C_{17}H_{15}N_2$ $(M+H)^+$: 247.1230, found: 247.1220; IR (Nujol): 1607, 1587, 1564, 1546, 1508, 1457, 1427, 1408, 1379, 1324, 1308, 1276, 1186, 1023, 834, 815, 759, 695, 650 cm^{-1}.
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