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COMMUNICATION

Convergent assembly of structurally diverse quinazolines†

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A convergent and versatile Vilsmeier–Haack-based carboannulation strategy that exhibits an unusually elevated bond-forming efficiency has been developed. By virtue of its innovative approach, structure economy and simple execution conditions the methodology reported here constitutes a very attractive protocol that enables the rapid assembly of structurally diverse quinazoline chemotypes.

Quinazolines represent an abundant heterocyclic nucleus that is present in diverse natural products[1] as well as a chemotype found in diverse therapeutic agents,[2] among which are the prominent drug molecules Prazosin, Gefitinib, Erlotinib, Afloqualone and Raltitrexed (Fig. 1). The pursuit of protein kinase inhibitors[3] has triggered renewed interest in molecular architectures that incorporate the quinazoline core. Paradoxically, a critical review of the relevant literature reveals that such a prolificacy in bioactive quinazoline entities is supported by collections of rather limited structural and functional diversity. Such data not only emphasize the enormous unexplored potential of quinazoline scaffolds in medicinal chemistry, but also highlight – the relevance of quinazolines notwithstanding – the fact that, although efficient, the compendium of preparative methods to access these heterobicyclic cores is somewhat limited.

As is common in heterocyclic synthesis praxis,[4] established preparative methods for the synthesis of quinazolines are based on the construction of the heterocyclic scaffold starting from appropriately functionalized *o*-disubstituted benzene derivatives (*e.g.* 2-aminobenzoic acids, 2-aminoarylketones, 2-aminobenzonitriles or isatoic anhydride),[4,5] those derived from Niementowsky synthesis[6] and Dimroth rearrangement[7] being particularly useful. A valuable incorporation to the synthetic armamentarium targeting the quinazoline nucleus has recently been published by Chilin,[8] which enables the rapid access to the heterobicyclic core from simple anilines after protection as ethyl carbamates. To the best of our knowledge, the opposite synthetic strategy (*i.e.* construction of the carbonated framework from the appropriate heterocyclic scaffold) has only been described occasionally.[9] Thus, the development of conceptually novel, convergent and practical quinazoline syntheses remains an unmet methodological challenge for organic chemists.

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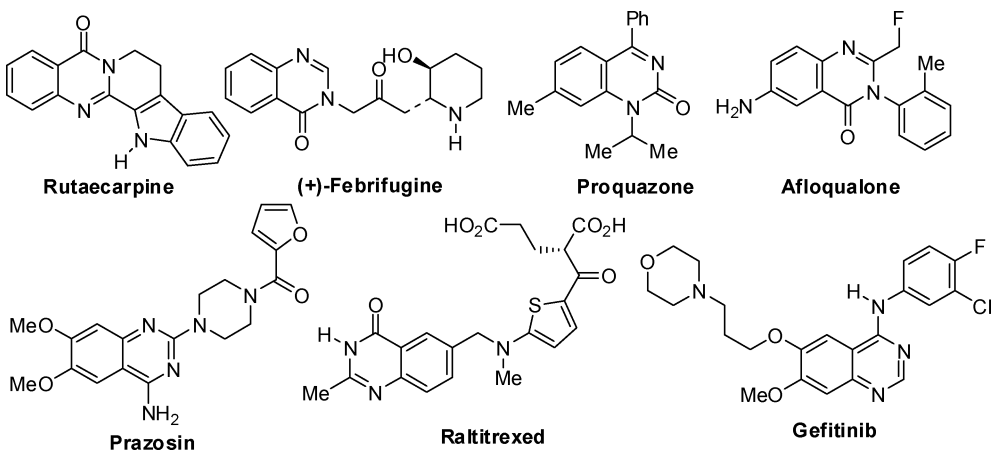


Fig. 1 Representative alkaloids and drugs incorporating the quinazoline scaffold.

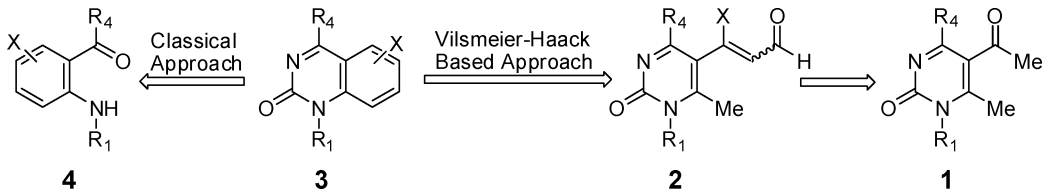
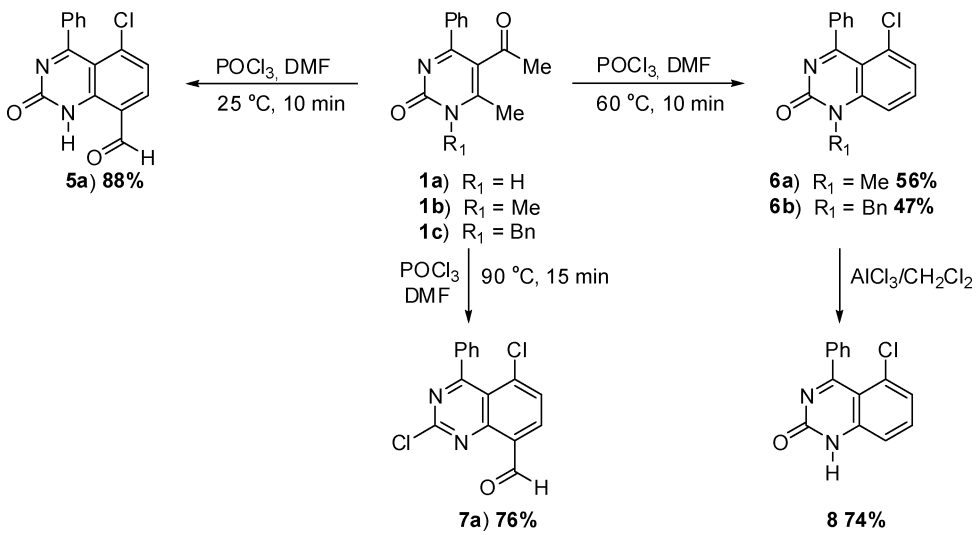


Fig. 2 Retrosynthetic scheme.

In the context of a lead optimization program on the pyrimidin-2(1*H*)-one framework it was required to experimentally validate *in silico* bioactivities predicted for virtually generated new ligands that incorporated a phenyl ring fused at positions 5,6 of the heterocyclic core [thus generating quinazolin-2(1*H*)-ones **3**]. Given our previous experience and the availability of collections of pyrimidin-2-(1*H*)-ones (readily accessible through Biginelli's condensation),[10] we considered the feasibility of an unprecedented carbo-annulation strategy starting from suitably substituted pyrimidin-2(1*H*)-ones (Fig. 2). It was envisioned that submitting 5-acetyl-6-methyl-4-arylpyrimidin-2(1*H*)-ones (**1**) to a Vilsmeier–Haack reaction[11] would afford β-chloroacroleins (**2**), which would undergo an intramolecular cyclization to provide a rapid assembly of target scaffolds (Fig. 2). Herein, we document an experimentally simple and versatile three-component reaction that enables rapid access to diverse sets of pharmacologically relevant chemotypes derived from the quinazoline scaffold. Moreover, the processes highlighted in this communication represent an unexplored one-pot pathway in which the heterobicyclic core is assembled through a Vilsmeier–Haack-assisted carbo-annulation strategy that employs readily accessible precursors and exhibits an unusually elevated bond-forming efficiency. This approach provide collections of significant structural and functional diversity in a time- and cost-effective manner.

The feasibility of the proposed sequence relies heavily on the efficacy of the halomethyleneiminium-mediated haloformylation of ketones that incorporate enolizable α-hydrogens.[12] Such a reaction would enable the transformation of the acetyl group at position 5 of the heterocycle into a vinyl halide that subsequently would add to an iminium group, thus extending the carbon framework by one unit and generating a highly reactive β-chloroacrolein (**2**). In order to prove this concept it was decided to employ pyrimidin-2(1*H*)-ones **1a–b** (Scheme 1, R_1 = H, Me) as model substrates. These compounds were submitted to the standard experimental conditions of the Vilsmeier–Haack reaction employing variable equivalents (1–10) of freshly distilled phosphorus oxychloride, different temperatures (0–90 °C) and reaction times (0.1–5 h).

Preliminary experimentation not only validated the feasibility of the proposed pathway in a shorter sequence, but also revealed remarkable facets of this chemistry that highlight its scope and versatility in terms of the rapid generation of molecular diversity (Scheme 1). The analytical and spectroscopic data (see supporting information) unequivocally showed that the products obtained during the Vilsmeier–Haack chloroformylation of **1a–b** are not the expected β-chlorovinyl aldehydes (**2**), but rather diverse chemotypes derived from the quinazoline scaffold (*e.g.* compounds **5**, **6** and **7**, Scheme 1). The structural assignment within the series (see supporting information) was complemented by X-ray crystallography data obtained on a monocrystal of one representative compound (compound **7b**, Fig. 3).[13] Remarkably, simple addition of freshly distilled phosphorus oxychloride to a solution of the heterocyclic substrate in dimethylformamide at a range of temperatures led to complete consumption of the staring material within relatively short reaction times (0.5–2 h). A detailed exploration of the transformation showed that slight modifications in the experimental conditions, particularly the reagent ratio and temperatures (see supporting information), led to either quinazolin-2(1*H*)-ones (**5** or **6**) or 3-chloroquinazolines (**7**).



Scheme 1 Vilsmeier–Haack-based carbo-annulation approach to quinazolines **5–8**.

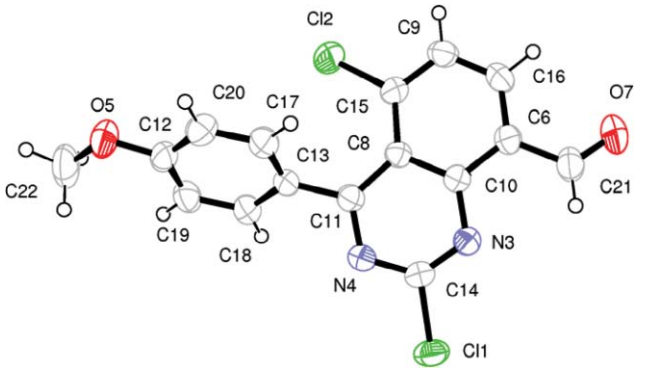
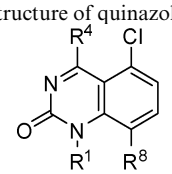


Fig. 3 Ortep plot showing the crystal structure and atomic numbering scheme for 2,5-dichloro-8-formyl-4-(4-methoxyphenyl)quinazoline (**7b**).

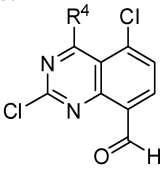
It was observed that some of the isolated compounds incorporate a formyl group at position 8 of the heterocyclic backbone (Scheme 1, compounds **5** and **7**), probably as a consequence of a post-annulation regiospecific Vilsmeier–Haack formylation. All attempts to avoid the formylation at the benzene moiety of the heterobicyclic core for the simplest model substrate [pyrimidin-2(1*H*)-one **1a**] failed, generating reaction mixtures in which the formylated products were the major components. Conversely, similar studies on the N-methyl analog (**1b**) revealed that formylation at position 8 of this substrate hardly occurs (even when working at high concentrations of the Vilsmeier–Haack reagent) and this process regiospecifically gave the non-formylated quinazolin-2(1*H*)-one **6b**. These data suggest strict control of the steric factors is required for the viability of the electrophilic aromatic substitution by the chloromethyleneiminium salt at position 8, but simultaneously provide valuable information from a mechanistic point of view.

In an attempt to broaden the scope of the methodology and to address access to non-formylated quinazolin-2(1*H*)-ones (**8**), and taking advantage of the decisive effect of steric hindrance at position 1 on reaction behavior, 5-acetyl-1-benzyl-6-methyl-4-aryl-3,4-dihydropyrimidin-2(1*H*)-one (**1c**) was submitted to the previously optimized experimental conditions (Scheme 1). It was gratifying to verify that this reaction satisfactorily afforded 2-benzyl-5-chloro-4-phenylquinolin-2(1*H*)-one (**6b**), thus confirming that the previously documented reactivity profile had been maintained. A mild cleavage protocol was employed to remove the benzyl group at position 1, thus validating the straightforward access to 5-chloro-4-arylquinolin-2(1*H*)-ones (**8**). Having established the feasibility of the proposed method for the model systems, and also having identified a set of optimal experimental conditions for each chemotype, the robustness and scope of the methodology was briefly assessed by employing a set of representative pyrimidin-2-ones **1** that incorporate different aryl groups at position 4 of the heterocyclic scaffold. These experiments provided additional evidence to support the versatility of the developed synthetic methodology (Table 1).

Table 1 Structure of quinazolines obtained



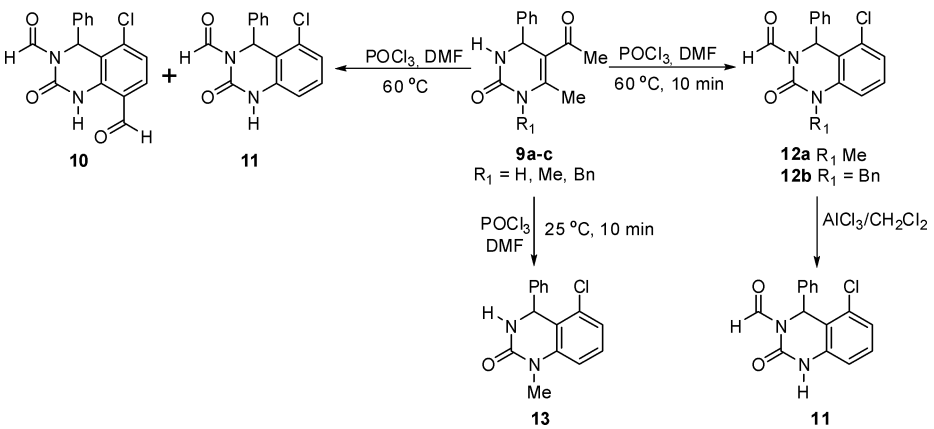
5, 6, 8



7

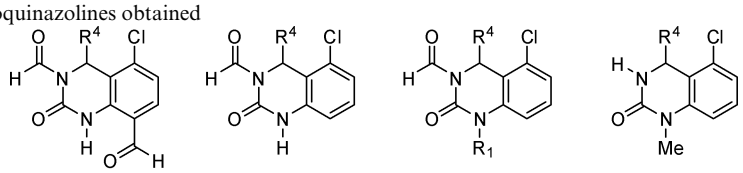
Compd	R^4	R^1	R^8	Yield
5a	Ph	H	CHO	88%
5b	Ph-4-OMe	H	CHO	65%
5c	Ph-4-Cl	H	CHO	50%
5d	Ph-4-Br	H	CHO	53%
6a	Ph	Me	H	56%
6b	Ph	Bn	H	47%
6c	Ph-4-OMe	Me	H	46%
6d	Ph-4-Cl	Me	H	53%
6e	Ph-4-Br	Me	H	50%
7a	Ph	—	—	76%
7b	Ph-4-OMe	—	—	58%
7c	Ph-4-Cl	—	—	63%
7d	Ph-4-Br	—	—	85%
8	Ph	H	H	74%

Encouraged by the excellent reactivity profiles and efficiency observed in the Vilsmeier–Haack-based carbo-annulation strategy within the pyrimidin-2(1*H*)-one series (**1**), we considered the feasibility of a similar sequence starting from the corresponding 3,4-dihydroanalogs (Scheme 2, compounds **9**). The experimental conditions evaluated, the model substrates (**9**) and the compounds isolated during this study (**10–13**) are shown in Scheme 2 and Table 2. As previously observed for the dehydroanalogs, complete consumption of the starting materials (**9**) was achieved within short reaction times (10–30 min) under Vilsmeier–Haack



Scheme 2 Vilsmeier–Haack-based carbo-annulation approach to 3,4-dihydroquinazolines **10–12**.

Table 2 Structures of 3,4-dihydroquinazolines obtained



10 **11** **12** **13**

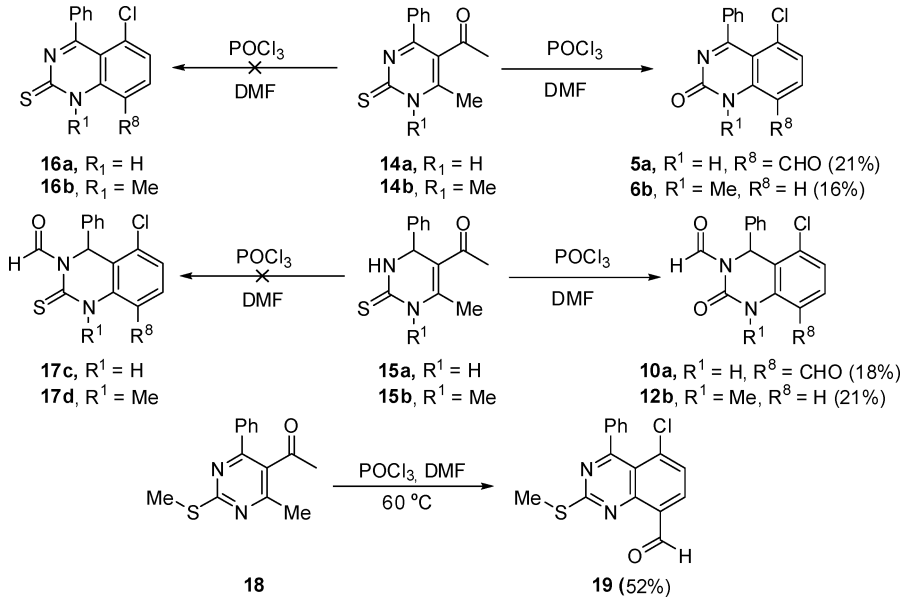
Compd	R^4	R^1	Yield
10a	Ph	H	56
10b	Ph-4-OMe	H	53
10c	Ph-4-Cl	H	60
10d	Ph-4-Br	H	57
11a	Ph	H	62
11b	Ph-4-OMe	H	55
11c	Ph-4-Cl	H	67
11d	Ph-4-Br	H	62
12a	Ph	Me	59
12b	Ph	Bn	66
12c	Ph-4-OMe	Me	53
12d	Ph-4-Cl	Me	58
12e	Ph-4-Br	Me	49
13	Ph	Me	53

conditions. While the carbo-annulation process showed a similar efficacy profile, slight modifications in reaction behaviour were observed (Scheme 2). Remarkably, within this series the heterocyclic scaffold is formylated at position 3 (Scheme 2), a predictable behaviour in the light of the well documented[14] nucleophilic profile of the N-3 atom of the 3,4-dihydropyrimidin-2(1*H*)-one scaffold. In agreement with previous findings for the pyrimidin-2(1*H*)-one series (**1**), the regiochemistry at position 8 (R_8 = H or CHO) is governed by the substitution pattern at position 1 (R_1 = H, Me or Bn) of the heterocyclic scaffold (Scheme 2). As corroborated by the spectroscopic and analytical data, concomitant formation of quinazolines **10** and **11** (typically in a 2 : 1 ratio) was observed on submitting **9a** to Vilsmeier–Haack conditions identical to those used for **1a** (see supporting information). An increased regioselectivity (4 : 1) in favor of the 3,8-diformylquinazoline-2-(1*H*)one **10** was obtained by modification of both the reagent ratio and temperature (see supporting information). As previously demonstrated for the pyrimidin-2(1*H*) series, regiospecific access to non-formylated quinazoline-2(1*H*)-ones **11** was provided by cleavage of the benzyl group at position 1 of **12b** employing aluminium chloride (Scheme 2). Fine tuning of the experimental conditions in these series also enabled the preparation of 5-chloro-1-methyl-4-phenyl-3,4-dihydroquinazolin-2(1*H*)-one **13** starting from **9b**. Once different experimental conditions to access the target quinazoline chemotypes were available, these were applied to a set of precursors that incorporated different aryl moieties at position 4 (Table 2). It can be seen (Scheme 2) that within the 3,4-dihydropyrimidin-2(1*H*)-one series the transformation retains its versatility and readily provides structurally and functionally diverse quinazoline frameworks (*i.e.* compounds **10–13**, Scheme 2).

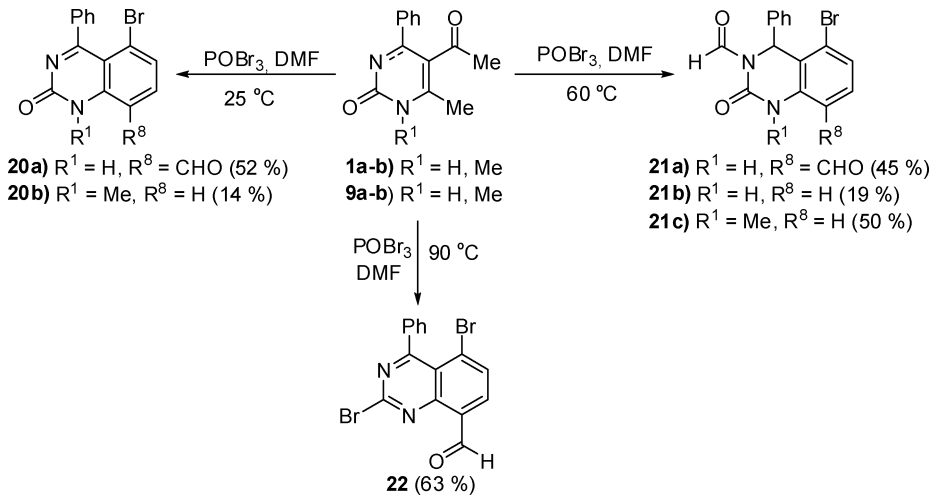
In an attempt to expand the scope of the strategy reported here, and taking advantage of the highly diverse collections of pyrimidine derivatives provided by the Biginelli reaction, we assessed the feasibility of a similar sequence but starting from 2-thioanalogs of previously tested substrates [*e.g.* pyrimidin-2(1*H*)-thiones **14a–b** and dihydroderivatives **15a–b**]. With this aim in mind, compounds **14–15** were reacted with dimethylformamide and phosphorus oxychloride under identical experimental conditions as for **1** and **9** (Scheme 3). In sharp contrast to the results described above, all experiments on these compounds afforded complex reaction mixtures from which, instead of the desired derivatives (**16** and **17**), low yields of the corresponding quinazolin-2(1*H*)-one or 3,4-dihydroquinazolin-2(1*H*)-one analogs (**5–6** and **10–12**) were isolated. As observed experimentally, the use of milder conditions [by performing the reactions at room temperature or below (0 °C) and/or employing preformed chloromethyleneiminium salt] did not have any effect on the reaction behavior. In an attempt to circumvent this drawback, it was decided to mask the thiocarbonyl moiety in the heterocyclic backbone by methylation. Thus, 1-[2-(methylthio)-4-methyl-6-phenylpyrimidin-5-yl]ethanone (**18**) was utilized as the reactive substrate under previously optimized experimental conditions of the Vilsmeier–Haack-based carbo-annulation strategy (Scheme 3). These experiments confirmed the feasibility of the sequence and successfully afforded the 5-chloro-8-formyl-2-methylthio-4-phenylquinazoline (**19**) in moderate yield (52%). Further work is now in progress in our laboratory aimed at extending this protocol to other 2-blocked pyrimidin-2(1*H*)-thiones, thus facilitating the thiocarbonyl reversion once the annulation process has finished.

To further challenge the Vilsmeier–Haack-based carbo-annulation strategy in terms of robustness and versatility, the possibility of increasing the diversity of the collections obtained by introducing a bromine atom[15] at positions 2 and 5 of the heterocyclic backbone was assessed (Scheme 4). With this aim, model substrates (**1a–b** and **9a–b**) were reacted with phosphorus oxybromide under previously optimized experimental conditions (Scheme 4). It was gratifying to find that both precursors rapidly underwent the Vilsmeier–Haack-assisted carbo-annulation to furnish the target structures (Table 1, **20–22**) and the previously observed reactivity profiles were maintained, albeit with a slightly reduced efficiency.

Although it is premature to propose a detailed mechanism at this stage, based on the above results a preliminary plausible mechanistic proposal for the herein documented



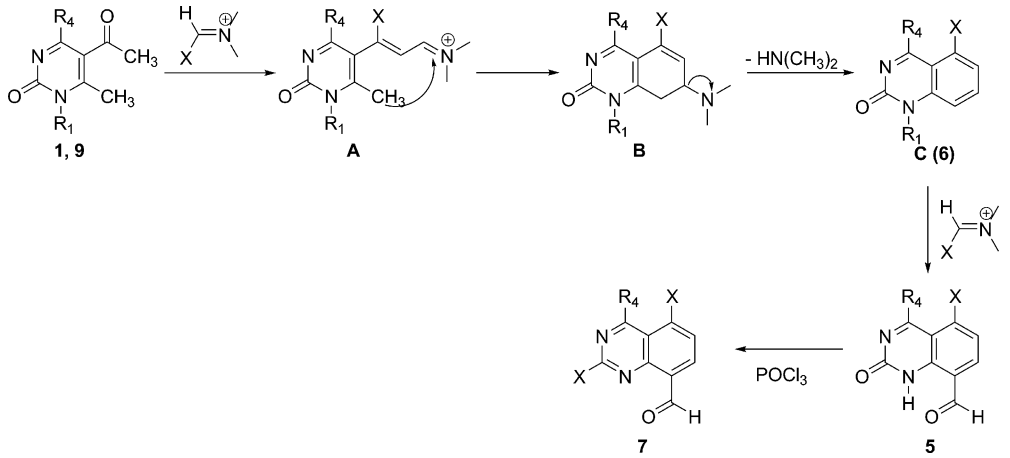
Scheme 3 Vilsmeier–Haack-based carbo-annulation approach to quinazoline **19**.



Scheme 4 Use of $POBr_3$ in the Vilsmeier–Haack-based carbo-annulation approach to quinazoline derivatives.

Vilsmeier–Haack–based carboannulation strategy is presented in Scheme 5. The overall transformation would start with the halogenation and subsequent addition of an iminium group to the acetyl group of the heterocycle, mediated by the Vilsmeier reagent, to generate a highly reactive β-halovinyliminium salt (**A**) which rapidly undergoes an intramolecular cyclization followed by elimination, thus generating the bicyclic heteroaromatic system (**C**). Once the carbo-annulation process has occurred – and depending on the substitution pattern at position 1 and the nature of the heterocycle (3,4-dihydro or aromatized) – the activated positions (*e.g.* 8 and/or 3) undergoes regioselective Vilsmeier–Haack formylation. Finally, high temperatures and excess of the reagent promotes the dehydrohalogenation of quinazoline-2-(1*H*)-ones **5** or **20a** to generate the corresponding 2-haloquinazolines (**7** or **22**).

The quinazoline synthesis reported here has two distinctive attributes derived from its intrinsic nature as a multicomponent reaction,[16] *e.g.* its high atom economy and inherent bond-forming efficiency. In particular, these processes elicit an unusually elevated bond-forming efficiency,[17] *i.e.* the number of bonds that are formed in one process. Some of the procedures described here involve the formation of up to 6 new bonds (7 if the *in situ* generation of the formylating reagent is considered) in a convergent and operationally simple synthetic methodology. An additional feature of the transformation concerns its contribution in terms of the rapid generation of skeletal and functional diversity (structure economy).[16] As can be seen, the role of the Vilsmeier–Haack reagent is not limited to its integration in the halocarbonated framework of the heterocyclic core. In addition, the synergistic exploitation of both the scaffold reactivity and variation of the experimental conditions enables the diversity contribution of the halomethyleneiminium salt to be maximized. This broad scope enables formyl and halogens (Cl or Br) to be incorporated at different positions of the quinazoline ring, both groups constituting



Scheme 5 Plausible mechanism of the herein described Vilsmeier–Haack-based carbo-annulation approach to quinazoline derivatives.

new reactive centres for additional diversification. Further work is in progress in our laboratories to study the biological activity of the herein described derivatives, as well as to evaluate the extension of this strategy to the synthesis of other heterobicyclic privileged scaffolds.

In summary, a convergent and versatile Vilsmeier–Haack-based carbo-annulation strategy that exhibits an unusually elevated bond-forming efficiency has been developed. By virtue of this innovative approach, structure economy, readily available starting materials, and simple conditions the herein documented methodology constitutes a very attractive protocol that enables the rapid assembly of collections of structurally diverse quinazoline chemotypes in a cost- and time-effective manner.

Representative procedure for the synthesis of quinazolines

To a solution of the corresponding 5-acetyl-6-methylpyrimidine derivative (**1**, **9**, or **18**) (10 mmol) in dimethylformamide (10 mL) was added freshly distilled phosphoryl oxychloride (30 mmol) and the reaction mixture stirred at the appropriate temperature. Once the reaction was complete, the mixture was allowed to reach room temperature, quenched by addition of water and evaporated *in vacuo*. The oily residue was added to ice and the aqueous layer was extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (2 × 20 mL), brine (2 × 20 mL) and dried over Na_2SO_4. The extracts were filtered through a pad of Celite and the solvent was removed on a rotary evaporator to give an oily residue, which was purified by chromatography on silica gel.

Acknowledgements

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