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# First $S_NAr$ reaction using TDAE-initiated carbanions in quinazoline series

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ABSTRACT

We report herein the first example of a $S_NAr$ reaction using TDAE-initiated carbanions in quinazoline series. The *o*-nitrobenzyl carbanion, formed by the action of TDAE on *o*-nitrobenzyl chloride, reacts with 4-chloro-2-trihalomethylquinazolines **4** and **5** via a $S_NAr$ mechanism. This enabled a new series of 4-benzyl-2-trihaloquinazoline derivatives to be synthesized in good yields under mild reaction conditions offering promising prospects for pharmacomodulation.



Since 2001, the 2-trihalomethylquinazoline scaffold has been intensively studied by medicinal chemists due to its large spectrum of biological activities, including anticancer properties.[1] Recently, our research team examined the anti-infectious potential of the 2-trichloromethylquinazoline scaffold. For the first time, several 4-substituted-2-trichloromethyl-quinazolines showed an activity against the W2 multi-resistant *Plasmodium falciparum* strain, combined with a safe toxicological profile (Fig. 1).[2] Some of these derivatives were obtained via an aromatic nucleophilic substitution on 4-chloro-2-trichloromethylquinazoline. With the aim of expanding the molecular diversity at position 4 of the quinazoline ring, we decided to replace the aniline moiety by a benzyl group for pharmacomodulation purposes.

With respect to 4-chloroquinazolines, the literature involving these substrates in $S_NAr$ reactions with various nucleophilic species such as thiolates,[3] ethanolates,[4] phenates[4] and amines[5] abounds, due to the highly electrophilic nature of position 4. However, very few examples of $S_NAr$ reactions between 4-chloroquinazolines and carbanions have been reported. These carbanions were generated from organomagnesian[6] species or from substrates with an activated methyl group and a strong base such as NaH, NaOEt or $NaNH_2$.[7] Because of the drastic conditions used in these methods, 4-benzylquinazolines are usually formed by cyclization of *N*-(2-(2-phenylacetyl)phenyl)acetamide.[8] To our knowledge, only one example of $S_NAr$ using benzylmagnesium bromide on 4-chloroquinazoline has been reported.[6] However, the potential reactivity of magnesium with the trichloromethyl group[9] prohibits their use in our study. Therefore, developing a selective methodology under milder conditions to perform $S_NAr$ reactions on 4-chloroquinazoline substrates with a wide range of benzylcarbanions could well be a new strategic option in the functionalization of the 4 position of the quinazoline ring.

Tetrakis(dimethylamino)ethylene (TDAE) is an organic reducing agent,[10] which reacts with haloalkyl derivatives to generate a carbanion under mild conditions.[11] Using this strategy, we have developed several reactions between nitrobenzylic substrates and various electrophilic species: firstly via nucleophilic addition with activated-carbonyl reagents,[12] and more recently, via nucleophilic substitution in α-halocarbonyl series.[13]

As part of ongoing research programme directed towards the development of original synthetic methods in medicinal chemistry,[14] we report herein the reactivity of various 4-chloro-2-trihalomethylquinazoline derivatives with nitrobenzylic carbanions formed in situ using the TDAE strategy.

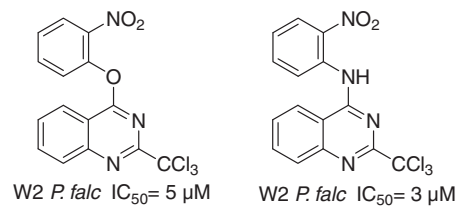


**Figure 1.** Structure of some 2-trichloromethylquinazolines displaying antiplasmodial activity.

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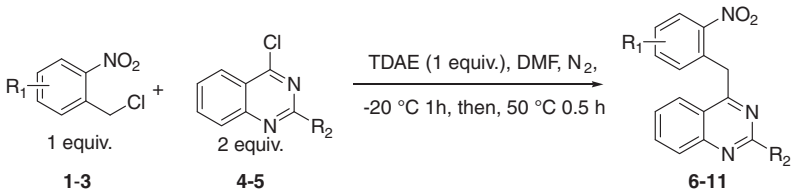
**Table 1**
Reaction of nitrobenzyl chlorides **1**–**3** with 4-chloroquinazolines **4**–**5** via the TDAE strategy




| Entry[a] | Nitrobenzyl chloride | $R_1$ | 4-Chloroquinazoline | $R_2$ | Product | Yield[b] (%) |
|---|---|---|---|---|---|---|
| 1 | **1** | H | **4** | $CCl_3$ | **6** | 83 |
| 2 | **2** | 5-$CH_3$ | **4** | $CCl_3$ | **7** | 80 |
| 3 | **3** | 4,5-$(OCH_3)_2$ | **4** | $CCl_3$ | **8** | 65 |
| 4 | **1** | H | **5** | $CF_3$ | **9** | 90 |
| 5 | **2** | 5-$CH_3$ | **5** | $CF_3$ | **10** | 87 |
| 6 | **3** | 4,5-$(OCH_3)_2$ | **5** | $CF_3$ | **11** | 45 |

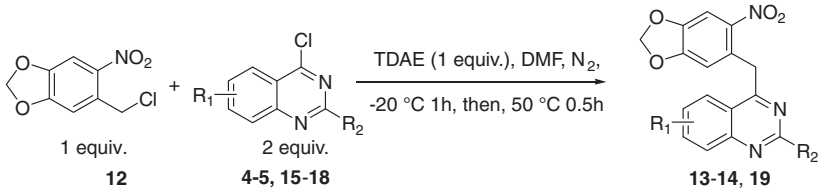
[a] Two equiv of quinazoline **4** or **5**, 1 equiv of *o*-nitrobenzyl chloride derivatives **1-3** and TDAE in anhydrous DMF stirred at −20 °C for 1 h and then heated to 50 °C for 30 min.
[b] % All yields refer to chromatographically isolated pure products and are relative to *o*-nitrobenzylchloride **1**–**3**.

*o*-Nitrobenzyl chloride derivatives (**1**–**3**) were added to 1 equiv of TDAE and 2 equiv of 4-chloro-2-trichloromethylquinazoline **4**[15] (Table 1) providing 4-(2-nitrobenzyl)-2-(trichloromethyl)quinazoline derivatives (**6–8**).[16] Reaction conditions (DMF, −20 °C for 1 h then heated to 50 °C for 0.5 h) were similar to previous conditions used in nucleophilic substitution between *o*-nitrobenzylic carbanions and α-halocarbonyl derivatives.[13] This methodology was then successfully extended to the synthesis of 4-(2-nitrobenzyl)-2-(trifluoromethyl)quinazoline (**9–11**)[16] from the commercially available 4-chloro-2-trifluoromethylquinazoline **5**. In both cases, yields were high and slightly better in trifluoromethyl series (65–83%/45–90%) except for the 1-(chloromethyl)-4,5-dimethoxy-2-nitrobenzene **3**. These experiments thus abundantly yielded the expected substitution products (**6–11**) in high yields.

In order to determine the scope and the limits of our methodology, we attempted to extend this reaction to various 4-chloroquinazoline compounds with 5-(chloromethyl)-6-nitrobenzo[*d*][1,3]dioxole **12** as the TDAE substrate (Table 2). These new quinazoline derivatives are either commercially available or prepared as previously described.[15,17]

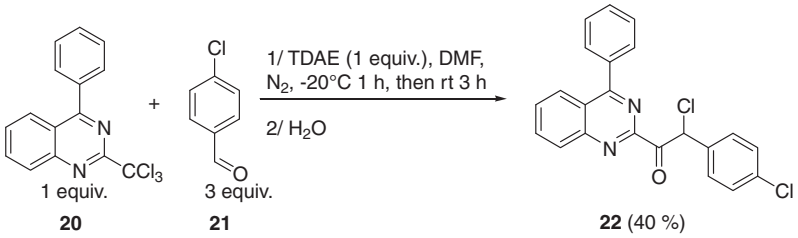
From quinazolines **4** and **5**, the 5-(chloromethyl)-6-nitrobenzo[*d*][1,3]dioxole **12** furnished the corresponding substitution products **13** and **14** in, respectively, 72 and 95% yield (Table 2, entries 7 and 8).[16] However, this methodology could not be generalized to 4-chloro-2-methylquinazoline **15,** 4-chloroquinazoline **16**. The 5-(chloromethyl)-6-nitrobenzo[*d*][1,3]dioxole **12** was reduced as 5-methyl-6-nitrobenzo[*d*][1,3]dioxole **20** in 55% (entry 9) to 76% (entry 10) yields. Only traces of the substitution products were isolated from ethyl 4-chloroquinazoline-2-carboxylate **17** (Table 2, entry 11). Finally, quinazoline **18** ($R_2$ = $CCl_3$) provided the substitution product **19** in 23% yield and 71% yield of the 5-(chloromethyl)-6-nitrobenzo[*d*][1,3]dioxole **12** was recovered unchanged.[18] This

**Table 2**
Reaction of nitrobenzyl chloride **12** with 4-chloroquinazolines **4**–**5**, **15**–**18**

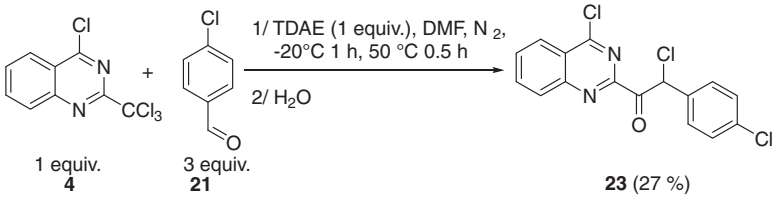



| Entry[a] | Quinazoline | $R_1$ | $R_2$ | Product | Yield[b] (%) |
|---|---|---|---|---|---|
| 7 | **4** | H | $CCl_3$ | **13** | 72 |
| 8 | **5** | H | $CF_3$ | **14** | 95 |
| 9 | **15** | H | $CH_3$ | — | 0[c] |
| 10 | **16** | H | H | — | 0[c] |
| 11 | **17** | H | COOEt | — | Traces[c] |
| 12 | **18** | 6-Cl | $CCl_3$ | **19** | 23[d] |

[a] Two equiv of quinazoline **4**–**5**, **15**–**18**, 1 equiv of *o*-nitrobenzyl chloride **12** and TDAE in anhydrous DMF stirred at −20 °C for 1 h and then warmed up to 50 °C for 30 min.
[b] % All yields refer to chromatographically isolated pure products and are relative to *o*-nitrobenzyl chloride **12**.
[c] Reduction product **20** is observed.
[d] Accompanied by the unchanged 5-(chloromethyl)-6-nitrobenzo[d][1,3]dioxole **12**.




**Scheme 1.** TDAE-initiated reaction of 2-trichloromethyl-quinazoline **20** with 4-chlorobenzaldehyde **21**.




**Scheme 2.** TDAE-initiated reaction of 2-trichloromethyl-quinazoline **4** with 4-chlorobenzaldehyde **21**.

uncompleted reduction of TDAE substrate **12** combined with numerous by-products could be explained by competition with the reducible nature of quinazoline **18**. We can note that in the reactions of quinazolines **15**–**18**, the quinazoline substrates are not recovered totally (20%) but associated with TDAE adducts.

The absence of reaction observed with quinazolines **15**–**17** led us to consider this reaction as electron withdrawing group-dependent. The substitution reaction seems to be correlated with the electropositive nature of the quinazoline 4-position ($-CF_3 > -CCl_3 > -COOEt$). Moreover, the carbanion formed via the TDAE methodology (stabilized by $TDAE^{++}$ counterion) was less reactive than a carbanion formed by an organometallic strategy.[19] The formation of reduction product **20** could be explained by the TDAE-initiated carbanion which was unable to give the substitution on the 4-chloro position, and was then reduced as derivative **20**. All these experimental data support a $S_NAr$ mechanism of an *o*-nitrobenzyl carbanion, formed via the action of the TDAE, on 4-chloro-2-trihalomethyl-quinazolines **4** and **5**.

Concerning the competitive reaction observed with trichloromethyl groups in TDAE strategy, we have previously demonstrated that a trichloromethyl group can react with the TDAE and aldehyde to form α-chloroketone derivatives.[20] To reveal the chemoselectivity of 4-chloro-2-trichloromethylquinazoline **4** under TDAE conditions, we first examined the ability of TDAE to reduce the 2-trichloromethyl group in quinazoline series. Thus, we subjected the 2-trichloromethylquinazoline **20**[2a] to 1 equiv of TDAE and 3 equiv of 4-chlorobenzaldehyde **21** at −20 °C for 1 h, followed by 2 h at rt which produced the expected α-chloroketone **22** in 40% yield (Scheme 1).[21]

The same reaction was observed by reacting 4-chloro-2-trichloromethylquinazoline **4** with aldehyde **21** under $S_NAr$ conditions providing α-chloroketone **23** in 27% yield (Scheme 2). This confirmed the TDAE reactivity of the 2-trichloromethyl group of **4** under these conditions[20] and may explain the competition observed with the TDAE reactivity between *o*-nitrobenzyl chloride **12** and 4-chloroquinazoline **18** (Table 2, entry 12).

In conclusion, we reported here the first example of a $S_NAr$ reaction using TDAE-initiated *o*-nitrobenzyl carbanions in 4-chloro-2-trihalomethylquinazolines series. Thus, a new series of 4-benzyl-2-trihalomethylquinazoline derivatives was synthesized in good yields under mild reaction conditions. Such an approach constitutes an original synthetic tool for conducting the functionalization of the 4 position of quinazoline scaffold. While this preliminary study reveals some drawbacks to this reaction it remains an easy, original and selective method to create a carbon–carbon bond despite the presence of a $CCl_3$ group. This work constitutes a good starting point towards the generalization of the $S_NAr$ reaction using TDAE-initiated carbanions in other series. Antiplasmodial evaluation of these new 4-(2-nitrobenzyl)-2-(trichloromethyl)quinazoline derivatives is currently underway.

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16. General procedure for the reaction of *o*-nitrobenzyl derivatives **1**–**3**, **12** and 4-chloro-2-trihalomethylquinazoline derivatives **4**–**5** using TDAE. Into a two-necked flask equipped with a nitrogen inlet were added, under nitrogen at −20 °C, 6 mL of anhydrous DMF solution of *o*-nitrobenzyl chloride derivatives (1 mmol, 1 equiv) and corresponding 2-trihalomethyl-4-chloroquinazoline derivatives. The solution was stirred and maintained at this temperature for 15 min and then the TDAE (1 equiv) was added dropwise via a syringe. A green to purple colour immediately developed with the formation of a white fine precipitate. The solution was vigorously stirred for 1 h and heated to 50 °C for 0.5 h. After this time, the crude was extracted with dichloromethane (50 mL), washed with water (3 × 100 mL) and dried with $Na_2SO_4$. Evaporation of the solvent left an orange to brown viscous liquid as the crude product. Purification was by silica gel chromatography ($CH_2Cl_2$/petroleum ether (8:2)). *4-(2-Nitrobenzyl)-2-trichloromethylquinazoline* (**6**). White solid, mp 168 °C, $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 5.16 (s, 2H, $CH_2$); 7.39–7.65 (m, 3H, 3×CH); 7.75–7.83 (m, 1H, CH); 7.96–8.04 (m, 1H, CH); 8.16–8.29 (m, 3H, 3×CH). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 38.6 ($CH_2$); 97.0 (C); 122.5 (C); 124.3 (CH); 125.2 (CH); 128.3 (CH); 129.5 (CH); 130.1 (CH); 131.8 (C); 133.2 (CH); 133.4 (CH); 134.7 (CH); 149.2 (C); 149.3 (C); 160.3 (C); 169.4 (C). Anal. Calcd for $C_{16}H_{10}Cl_3N_3O_2$: C, 50.22; H, 2.63; N, 10.98. Found: C, 49.69; H, 2.69; N, 10.80. *4-(5-Methyl-2-nitrobenzyl)-2-trichloromethylquinazoline* (**7**). Yellow solid, mp 161 °C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 2.40 (s, 3H, $CH_3$); 5.13 (s, 2H, $CH_2$); 7.22–7.28 (m, 2H, 2×CH); 7.74–7.82 (m, 1H, CH); 7.95–8.03 (m, 1H, CH); 8.07–8.29 (m, 3H, 3×CH). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 21.4 ($CH_3$); 38.6 ($CH_2$); 97.0 (C); 122.5 (C); 124.3 (CH); 125.4 (CH); 128.8 (CH); 129.5 (CH); 130.0 (CH); 131.7 (C); 133.8 (CH); 134.6 (CH); 144.6 (C); 146.9 (C); 149.3 (C); 160.2 (C); 169.6 (C). Anal. Calcd for $C_{17}H_{12}Cl_3N_3O_2$: C, 51.48; H, 3.05; N, 10.59. Found: C, 50.83; H, 3.05; N, 10,59. *4-(4,5-Dimethoxy-2-nitrobenzyl)-2-trichloromethylquinazoline* (**8**). Yellow solid, mp 180 °C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 3.89 (s, 3H, $CH_3$); 3.95 (s, 3H, $CH_3$); 5.10 (s, 2H, $CH_2$); 6.92 (s, 1H, CH); 7.73–7.79 (m, 2H, 2×CH); 7.92–8.01 (m, 1H, CH); 8.13–817 (m, 1H, CH); 8.25–8.29 (m, 1H, 1CH). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 38.1 ($CH_2$); 56.2 ($CH_3$); 56.3 ($CH_3$); 97.1 (C); 108.2 (CH); 114.5 (CH); 122.4 (C); 124.3 (CH); 126.5 (C); 129.5 (CH); 129.9 (CH); 134.6 (CH); 141.3 (C); 147.8 (C); 149.2 (C); 153.0 (C); 160.1 (C); 169.8 (C). Anal. Calcd for $C_{18}H_{14}Cl_3N_3O_4$: C, 48.84; H, 3.19; N, 9.49. Found: C, 48.75; H, 3.25; N, 9.42. *4-(2-Nitrobenzyl)-2-trifluoromethylquinazoline* (**9**). White solid, mp 155 °C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 5.12 (s, 2H, $CH_2$); 7.35–7.39 (m, 1H, CH); 7.45–7.64 (m, 2H, 2×CH); 7.78–7.86 (m, 1H, CH); 7.98–8.07 (m, 1H, CH); 8.12–8.30 (m, 3H, 3×CH). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 38.5 ($CH_2$); 120.7 (q, $J$ = 275.6 Hz, $CF_3$); 123.8 (C); 124.4 (CH); 125.2 (CH); 128.4 (CH); 129.9 (2×CH); 131.6 (C); 133.1 (CH); 134.4 (CH); 134.9 (C); 149.2 (C); 149.5 (C); 151.9 (q, $J$ = 36.2 Hz, C); 169.6 (C). Anal. Calcd for $C_{16}H_{10}F_3N_3O_2$: C, 57.66; H, 3.02; N, 12.61. Found: C, 58.23; H, 2.97, N, 12.42. *4-(5-Methyl-2-nitrobenzyl)-2-trifluoromethyl-quinazoline* (**10**). White solid, mp 147 °C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 2.40 (s, 3H, $CH_3$); 5.10 (s, 2H, $CH_2$); 7.16 (s, 1H, CH); 7.24–7.29 (d, 1H, CH); 7.77–7.85 (m, 1H, CH); 7.98–8.09 (m, 2H, 2×CH); 8.18–8.30 (m, 2H, 2×CH). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 21.4 ($CH_3$); 38.6 ($CH_2$); 119.7 (q, $J$ = 275.6 Hz, $CF_3$); 123.8 (C); 124.5 (CH); 125.4 (CH); 129.0 (CH); 129.9 (CH); 130.0 (CH); 131.4 (C); 133.7 (CH); 134.8 (CH); 144.7 (C); 146.8 (C); 149.5 (C); 151.9 (q, $J$ = 36.2 Hz, C); 169.8 (C). Anal. Calcd for $C_{17}H_{12}F_3N_3O_2$: C, 58.79; H, 3.48; N, 12.10. Found: C, 59.49; H, 3.52; N, 12.07. *4-(4,5-Dimethoxy-2-nitrobenzyl)-2-trifluoromethylquinazoline* (**11**). Yellow solid, mp 170 °C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 3.92 (s, 3H, $CH_3$); 3.97 (s, 3H, $CH_3$); 5.09 (s, 2H, $CH_2$); 6.92 (s, 1H, CH); 7.73 (s, 1H, CH); 7.78–7.86 (m, 1H, CH); 7.98–8.06 (m, 1H, CH); 8.17–8.22 (m, 1H, CH); 8.32–8.36 (m, 1H, CH). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 38.0 ($CH_2$); 56.3 (2×$CH_3$); 108.3 (CH); 114.7 (CH); 119.8 (q, $J$ = 275.6 Hz, C); 123.9 (C); 124.6 (CH); 126.2 (C); 129.9 (2×CH); 134.9 (CH); 141.2 (C); 148.0 (C); 149.5 (C); 151.9 (q, $J$ = 36.6 Hz, C); 153.1 (C); 170.1 (C). Anal. Calcd for $C_{18}H_{14}F_3N_3O_4$: C, 54.97; H, 3.59; N, 10.68. Found: C, 55.80; H, 3.64; N, 10.60. *4-((6-Nitrobenzo[d][1,3]dioxol-5-yl)methyl)-2-trichloromethylquinazoline* (**13**). Yellow solid, mp 193 °C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 5.08 (s, 2H, $CH_2$); 6.14 (s, 2H, $CH_2$); 6.82 (s, 1H, CH); 7.70 (s, 1H, CH); 7.74–7.83 (m, 1H, CH); 7.96–8.04 (m, 1H, CH); 8.18–8.27 (m, 2H, 2×CH). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 39.9 ($CH_2$); 97.0 (C); 103.0 ($CH_2$); 106.0 (CH); 111.7 (CH); 122.4 (C); 124.2 (CH); 128.8 (C); 129.5 (CH); 130.0 (CH); 134.7 (CH); 143.0 (C); 147.2 (C); 149.3 (C); 151.9 (C); 160.3 (C); 169.5 (C). Anal. Calcd for $C_{17}H_{10}Cl_3N_3O_4$: C, 47.86; H, 2.36; N, 9.85. Found: C, 47.90; H, 2.34; N, 9.79. *4-((6-Nitrobenzo[d][1,3]dioxol-5-yl)methyl)-2-trifluoromethylquinazoline* (**14**). Yellow solid, mp 208 °C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 5.04 (s, 2H, $CH_2$); 6.13 (s, 2H, $CH_2$); 6.76 (s, H, CH); 7.67 (s, H, CH); 7.77–7.85 (m, 1H, CH); 7.98–8.06 (m, 1H, CH); 8.19–8.29 (m, 2H, 2×CH). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 38.8 ($CH_2$); 103.1 ($CH_2$); 106.1 (CH); 111.8 (CH); 119.8 (q, $J$ = 275.9 Hz, C); 123.8 (C); 124.5 (CH); 128.5 (C); 129.9 (CH); 130.0 (CH); 134.9 (CH); 142.9 (C); 147.4 (C); 149.5 (C); 152.0 (C); 152.1 (q, $J$ = 36.6 Hz, C); 169.8 (C). Anal. Calcd for $C_{17}H_{10}F_3N_3O_4$: C, 54.12; H, 2.67; N, 11.14. Found: C, 54.58; H, 2.65, N, 11.04.
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18. *4,6-Dichloro-2-trichloromethylquinazoline* (**18**) White solid, mp 172 °C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.00 (dd, $J$ = 9,0 Hz, $J$ = 2.2 Hz, 1H, CH); 8.17 (d, $J$ = 9.0 Hz, 1H, CH); 9.33 (d, $J$ = 2.2 Hz, 1H, CH). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 95.6 (C); 123.5 (C); 124.9 (CH); 131.3 (CH); 136.9 (C); 137.0 (CH); 148.6 (C); 160.1 (C); 163.0 (C). Anal. Calcd for $C_9H_3Cl_5N_2$: C, 34.16; H, 0.96; N, 8.85. Found: C, 34.15; H, 0.94; N, 8.57. *6-Chloro-4-((6-nitrobenzo[d][1,3]dioxol-5-yl)methyl)-2-trichloromethylquinazoline* (**19**). White solid, mp 206 °C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 5.02 (s, 2H, $CH_2$); 6.16 (s, 2H, $CH_2$); 6.83 (s, 1H, CH); 7.73 (s, 1H, CH); 7.91–7.97 (m, 1H, CH); 8.13–8.17 (m, 1H, CH); 8.24–8.25 (m, 1H, CH). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 39.3 ($CH_2$); 96.7 (C); 103.1 ($CH_2$); 106.2 (CH); 111.9 (CH); 123.0 (C); 123.4 (CH); 128.3 (C); 131.6 (CH); 135.5 (C); 135.7 (CH); 143.0 (C); 147.4 (C); 147.8 (C); 152.1 (C); 160.5 (C); 168.9 (C). Anal. Calcd for $C_{17}H_9Cl_4N_3O_4$: C, 44.28; H, 1.97; N, 9.11. Found: C, 43.75; H, 1.87; N, 8.91.
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21. *Procedure for the reaction of 4-chloro- or 4-phenyl-2-trichloro methylquinazoline and 4-chlorobenzaldehyde using TDAE.* Into a two-necked flask equipped with a nitrogen inlet were added, under nitrogen at −20 °C, 6 mL of anhydrous DMF solution of 2-trihalomethyl-4-chloroquinazoline (1 mmol, 1 equiv) and 4-chlorobenzaldehyde (3 mmol, 3 equiv). The solution was stirred and maintained at this temperature for 15 min and then the TDAE (1 equiv) was added dropwise via a syringe. An orange colour immediately developed with the formation of a white fine precipitate. The solution was vigorously stirred for 1 h and heated slowly to rt over 3 h or 50 °C over 0.5 h. After this time, the crude was extracted with dichloromethane (50 mL), washed with water (3 × 100 mL) and dried with $Na_2SO_4$. Evaporation of the solvent left an orange to brown viscous liquid as the crude product. Purification was by silica gel chromatography ($CHCl_3$). *2-Chloro-2-(4-chlorophenyl)-1-(4-phenylquinazolin-2-yl)ethanone* (**22**). Yellow solid, mp 89 °C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.22 (s, 1H, CH); 7.27–7.31 (m, 2H, 2×CH); 7.54–7.61 (m, 5H, 5×CH); 7.70–7.79 (m, 3H, 3×CH); 7,95–8.04 (m, 1H, CH); 8.20–8.16 (m, 1H, CH); 8.25–8.29 (m, 1H, CH). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$. 61.3 (CH); 123.3 (C); 127.2 (CH); 128.7 (2×CH); 129.0 (2×CH); 130.2 (3×CH); 130.3 (CH); 130.6 (2×CH); 134.2 (C); 134.5 (CH); 135.0 (C); 136.4 (C); 151.0 (C); 154.0 (C); 169.4 (C); 190.4 (C). RMS (EI): calcd for $C_{22}H_{14}Cl_2N_2O$ $[M]^+$: 392.0; found, 392.0. *2-Chloro-2-(4-chlorophenyl)-1-(4-chloroquinazolin-2-yl)ethanone* (**23**). Beige solid, mp 171 °C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.08 (s, 1H, CH); 7.31 (d, $J$ = 8.5 Hz, 2H, 2×CH); 7.55 (d, $J$ = 8.5 Hz, 2H, 2×CH); 7.84–7.93 (m, 1H, CH); 8.04–8.12 (m, 1H, CH); 8.21–8.26 (m, 1H, CH); 8.32–8.36 (m, 1H, CH). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 60.9 (CH); 124.3 (C); 126.1 (CH); 129.2 (2×CH); 130.0 (CH); 130.6 (2×CH); 131.6 (CH); 133.6 (C); 135.3 (C); 135.9 (CH); 150.5 (C); 153.3 (C); 164.0 (C); 188.9 (CO). HR-MS calcd for $C_{16}H_9Cl_3N_2O$ $[M+H]^+$: 350.9853, found: 350.9850.