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Symmetrical Trichlorotriazine Derivatives as Efficient Reagents for One-Pot Synthesis of 3-Acetyl-2-chloroquinolines from Acetanilides under Vilsmeier–Haack Conditions

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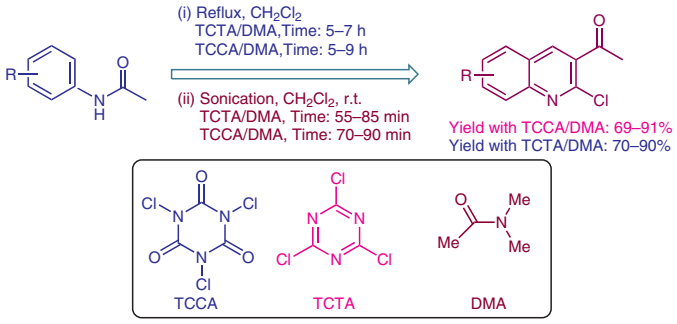

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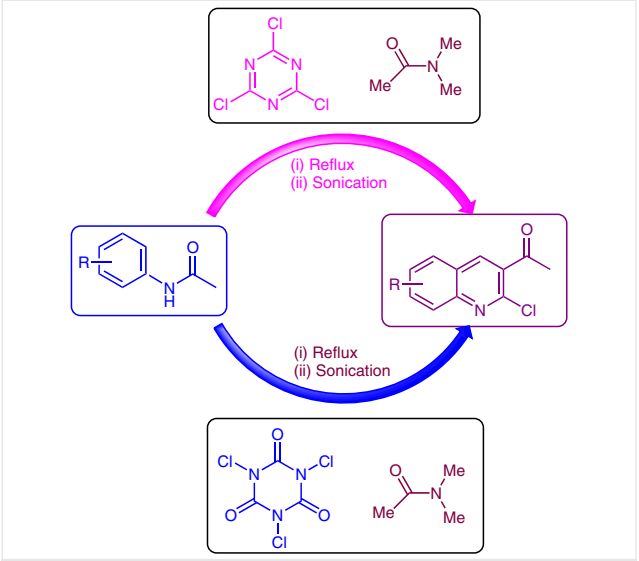
Abstract Symmetrical trichlorotriazine derivatives such as 2,4,6-trichloro-1,3,5-triazine and trichloroisocyanuric acid were explored as Vilsmeier–Haack type reagents in the presence of *N*,*N*-dimethylacetamide for the effective synthesis of 3-acetyl-2-chloroquinolines from acetanilides. Ultrasonication led to shorter reaction times than conventional heating and gave yields comparable to those obtained under reflux conditions.

Key words trichlorotriazines, Vilsmeier–Haack reaction, acetanilides, chloroacetylquinolines, sonication

Quinolines form an important group of heterocyclic compounds that have been found to exhibit bactericidal, antitumor, antimalarial, antiinflammatory, and antiviral activities.[1–8] More specifically, 3-acetyl-2-chloroquinolines occupy a prominent position among the family of quinolines, as they are key intermediates for the synthesis of thieno[2,3-*b*]quinolines. In an earlier publication, Bhat and Bhaduri reported a synthesis of quinolines involving two or three steps.[8] In our earlier papers, we have reported a one-pot synthesis of formyl- and acetylquinolines from acetanilides under Vilsmeier–Haack conditions[9–11] by using *N*,*N*-dimethylacetamide (DMA)/$POCl_3$. *N*,*N*-Dialkyl amides (DMF or DMA) and oxychlorides such as phosphoryl chloride, thionyl chloride, or phosgene form chloromethyleniminium salts in situ.[11–16] However, oxychlorides are moisture sensitive and toxic.

Efforts have been made to avoid the use of oxychlorides by replacing them with 2,4,6-trichlorotriazine (cyanuric chloride, TCTA)[17,18] to give the corresponding DMF adducts as alternative Vilsmeier–Haack reagents. Symmetrical 1,3,5-triazine derivatives have also been used to promote transformations such as Friedel–Crafts acylations, Beckman rearrangements, Lossen rearrangements, carboxylic-acid activations, and Swern oxidations.[19–27]

Encouraged by these results, we embarked on a comparative study using two different adducts of DMA with TCTA or trichloroisocyanuric acid (1,3,5-trichloro-1,3,5-triazinane-2,4,6-trione, TCCA) for the synthesis of 3-acetylquinolines through simultaneous cyclization and acetylation of acetanilides under conventional and ultrasonically assisted conditions (Scheme 1).



Scheme 1 Synthesis of 3-acetyl-2-chloroquinolines from acetanilides by using TCTA/DMA or TCCA/DMA as Vilsmeier–Haack reagents

With conventional heating at the reflux in CH_2Cl_2, reaction times for most of the studied reactions were in the range five to nine hours, depending on the structure of the acetanilide and reagent used (Table 1).

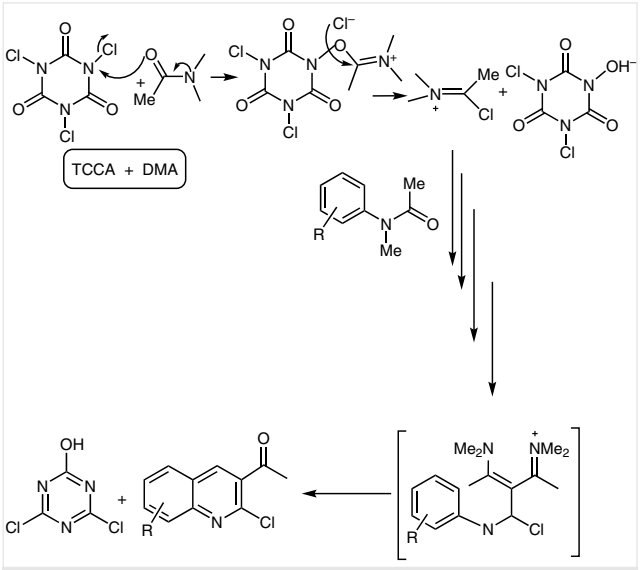
Table 1 Synthesis of 3-Acetyl-2-chloroquinolines from Acetanilides by Using TCTA/DMA or TCCA/DMA as a Vilsmeier–Haak Reagent[a]

Entry	Acetanilide	Product	TCCA		TCTA	
			Time (h)	Yield (%)	Time (h)	Yield (%)
1	acetanilide	3-acetyl-2-chloroquinoline	7	85	8	80
2	4-bromoacetanilide	3-acetyl-6-bromo-2-chloroquinoline	6	85	7	80
3	2-chloroacetanilide	3-acetyl-2,8-dichloroquinoline	8	85	8	85
4	4-chloroacetanilide	3-acetyl-2,6-dichloroquinoline	7	90	6	90
5	4-methoxyacetanilide	3-acetyl-2-chloro-6-methoxyquinoline	6	91	5	89
6	4-nitroacetanilide	3-acetyl-2-chloro-6-nitroquinoline	8	75	9	72
7	3-nitroacetanilide	3-acetyl-2-chloro-7-nitroquinoline	7	69	8	70
8	4-methylacetanilide	3-acetyl-2-chloro-6-methylquinoline	5	82	5	80
9	2-ethylacetanilide	3-acetyl-2-chloro-8-ethylquinoline	5	87	6	86
10	2-nitroacetanilide	3-acetyl-2-chloro-8-nitroquinoline	6	85	7	85

[a] Reaction conditions: acetanilide (9.8 mmol), TCCA/DMA or TCTA/DMA,[32] CH_2Cl_2 (50 mL), reflux.

The mechanism of the reaction can be explained through the formation of TCTA/DMA or TCCA/DMA adducts containing a chloromethyleniminum moiety. The formation of a chloromethyleniminum cation intermediate is supported by spectroscopic observations. In the IR spectrum of the TCCA/DMA adduct, absorption bands associated with the starting materials showed marked shifts, significant absorptions being observed at 3215 (broad), 1706 (broad), and 1750 (weak) cm^{-1}. These observations are largely similar to those in our earlier reports on the formation of TCTA/DMF and TCCA/DMF adducts, respectively.[29,30]

The chloromethyleniminum cation thus formed reacts with the acetanilide to afford 3-acetyl-2-chloroquinolines. (Spectroscopic data for the isolated 3-acetyl-2-chloroquinolines are given in supplementary data.) The results in Table 1 show that the reactions using both TCTA/DMA and TCCA/DMA adducts[31] were too sluggish under conventional reflux conditions.[32] However, under sonication at r.t.,[33] the reaction times were reduced significantly from 5–9 hours to 35–90 minutes (Table 2).



Scheme 2 Mechanism of the formation of 3-acetyl-2-chloroquinolines from acetanilide by using the TCCA/DMA Vilsmeier–Haack adduct

Table 2 Ultrasonically Assisted Synthesis of 3-Acetyl-2-chloroquinolines from acetanilides by Using TCTA/DMA or TCCA/DMA as a Vilsmeier–Haak Reagent[a]

Entry	Acetanilide	Product	TCCA		TCTA	
			time (min)	Yield (%)	Time (min)	Yield (%)
1	acetanilide	3-acetyl-2-chloroquinoline	75	85	80	80
2	4-bromoacetanilide	3-acetyl-6-bromo-2-chloroquinoline	85	85	90	85
3	2-chloroacetanilide	3-acetyl-2,8-dichloroquinoline	80	80	91	79
4	4-chloroacetanilide	3-acetyl-2,6-dichloroquinoline	75	85	85	85
5	4-methoxyacetanilide	3-acetyl-2-chloro-6-methoxyquinoline	60	89	60	90
6	4-nitroacetanilide	3-acetyl-2-chloro-6-nitroquinoline	65	85	65	85

Table 2 (continued)

Entry	Acetanilide	Product	TCCA		TCTA	
			time (min)	Yield (%)	Time (min)	Yield (%)
7	3-nitroacetanilide	3-acetyl-2-chloro-7-nitroquinoline	70	81	70	79
8	4-methylacetanilide	3-acetyl-2-chloro-6-methylquinoline	60	85	60	80
9	2-ethylacetanilide	3-acetyl-2-chloro-8-ethylquinoline	55	90	55	90
10	2-nitroacetanilide	3-acetyl-2-chloro-8-nitroquinoline	70	85	75	80

[a] Reaction conditions: acetanilide (9.8 mmol), TCCA/DMA or TCTA/DMA,[33] CH_2Cl_2 (50 mL), ultrasound, r.t.

In summary, we have developed TCCA/DMA and TCTA/DMA adducts as efficient modified Vilsmeier-Haack reagents for the effective synthesis of 3-acetyl-2-chloroacetylquinolines from acetanilides. The reactions afforded good yields and, depending on the structure of the acetanilide, reaction times recorded were reduced from 5–9 hours under conventional conditions to 55–85 minutes under sonication. Even the most sluggish reactant (4-nitroacetanilide) underwent rate acceleration from 8–9 hours to 65 minutes. Product yields are also increased under sonication as compared with conventional heating.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1589099.

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(31) **TCTA/DMA and TCCA/DMA Reagents**
TCTA or TCCA (0.110 mol) and DMA (0.13 mol) were added to CH_2Cl_2 (50 mL) in a round-bottomed flask and the mixture was stirred for about 3 h at r.t. to give a white precipitate.
(32) **Cyclization/Acetylation of Acetanilides by Using TCTA/DMA or TCCA/DMA; General Procedure**
The appropriate acetanilide (9.8 mmol) was added to the TCTA/DMA or TCCA/DMA reagent, prepared as above, and the mixture was stirred constantly under reflux. When the reaction was complete (TLC), H_2O (50.0 mL) was added, and the mixture was stirred to extract the inorganic components into the H_2O and the crude product into the organic layer. The crude product was purified by column chromatography [Merck Silica Gel 60 (230–400 mesh), EtOAc–hexane].
(33) **Cyclization/Acetylation of Acetanilides by Using TCTA/DMA or TCCA/DMA with Sonication; General Procedure**
The method for the ultrasonically assisted reactions was similar to the classical method. The flask containing the reaction mixture, prepared as detailed above, was placed in a sonicator (KQ-250B; Kunshan Ultrasonic Instruments, Kunshan) at r.t., and the progress of the reaction was monitored by TLC. The product was separated and worked up by similar procedure to that described above.
3-Acetyl-2-chloroquinoline (Tables 1 and 2, entry 1) solid; yield: (85%); mp 74–76 °C (Lit. 75–76 °C); IR (KBr): 1705 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.70 (s, 3 H, $COCH_3$), 7.0–8.25 (m, 5 H, arom). MS ESI: *m/z* = 205 [M^+].