# Synthesis of 1,3,5-Triacylperhydro-1,3,5-triazines Catalyzed by Ion-Exchange Resins

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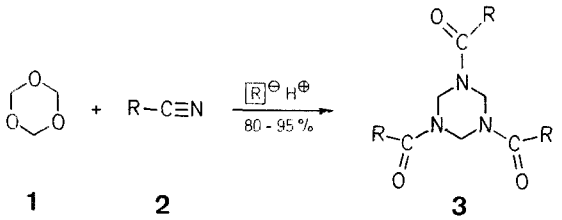
1,3,5-Triacylperhydro-1,3,5-triazines can be obtained in high yields by reaction of 1,3,5-trioxan with nitriles in solvents such as chlorobenzene using as catalyst an ion-exchange resin such as Amberlyst 15® with precise control of the hydration rate of the resin.

1,3,5-Triacylperhydro-1,3,5-triazines are widely used in the chemical industry and their synthesis has repeatedly been the subject of investigations[1-6]. The main method for the synthesis of the title compounds is the reaction of nitriles with formaldehyde in an acidic medium. The use of concentrated sulfuric acid may lead to insufficient selectivity of the reactions. For the reaction of 1,3,5-trioxan (trimeric formaldehyde) with a variety of nitriles, the use of a mixture of *p*-toluenesulfonic acid, sulfuric acid, and acetic anhydride as catalyst has been suggested[3]. This modification improves the yield of 1,3,5-triacylperhydro-1,3,5-triazines but it does not completely inhibit degradation reactions which may proceed in such a medium.

We describe here a novel modification of the synthesis of 1,3,5-triacylperhydro-1,3,5-triazines **(3)** from 1,3,5-trioxan (paraformaldehyde, **1**) and nitriles **(2)** which uses as catalysts cation-exchange resins with careful control of their hydration rate. The reaction is performed in an organic solvent such as chlorobenzene which mainly acts as an extractor which avoids direct and permanent contact between the heterocycle **3** and acidic groups[6] and which plays a role with regard to the diffusion levels of the reactive components in the pores of the resin.




**1** **2** **3**

[R] = resin

Of all ion-exchange resins tested, macroporous resinsulfonic acids in the acid form proved to be the most effective catalysts.

The new modification described here makes possible the synthesis under mild conditions of the 1,3,5-triazine derivatives **3**, most of which are difficult to prepare in a homogeneous medium.

The hydration rates of the ion-exchange resins are determined using Karl Fisher's classical titration technique[6], adapted to this type of material.

**1,3,5-Triacylperhydro-1,3,5-triazines (3), General Procedure:**
Chlorobenzene (100 ml), Amberlyst 15® resin (10 g; hydration rate: 120 mg water/g dry resin) (The same results can be obtained with Lewatit® Bayer resins SPC 108, SPC 112, and SPC 120), and the

**Table 1.** 1,3,5-Triacylperhydro-1,3,5-triazines (**3**) Prepared

| 3 | R | Reaction Time [h] | Yield[a] [%] | m.p. [°C] | Molecular Formula[b] or m.p. [°C] reported |
|---|---|---|---|---|---|
| **a** | $CH_3$ | 20 | 80 | 72° | – |
| **b** | $C_2H_5$ | 1.5 | 95 | 170° | $C_{12}H_{21}N_3O_3$ (255.3) |
| **c** | $H_2C{=}CH{-}$ | 4 | 95 | – | $C_{12}H_{15}N_3O_3$ (249.2) |
| **d** | $ClCH_2{-}CH_2{-}$ | 2 | 84 | 172° | $C_{12}H_{18}ClN_3O_3$ (358.6) |
| **e** | $H_3CO{-}CH_2{-}CH_2{-}$ | 6 | 90 | 150° | $C_{15}H_{27}N_3O_6$ (345.3) |
| **f** | $n$-$C_3H_7$ | 10 | 90 | 94° | $C_{15}H_{27}N_3O_3$ (297.4) |
| **g** | $C_6H_5$ | 20 | 95 | 220° | – |

[a] Yield of isolated pure product.

[b] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.31; H, ±0.35; N, ±0.34. Exceptions: **3b**, C, −0.43; H, +0.56; N, −0.43; **3e**, H, −0.53.

**Table 2.** Spectral Data of Compounds **3**

| 3 | I.R. (KBr) $\nu_{C=O}$ [$cm^{-1}$] | $^1$H-N.M.R. ($CDCl_3$/$TMS_{int}$) $\delta$ [ppm] of N—$CH_2$—N | $^{13}$C-N.M.R. ($CDCl_3$/$TMS_{int}$) $\delta$N—$CH_2$—N | $\delta$C=O [ppm] |
|---|---|---|---|---|
| **a** | 1640 | 5.29 | 56.57 | 169.91 |
| **b** | 1640 | 5.35 | 55.92 | 173.08 |
| **c** | 1620–1645 | 5.44 | 56.64 | 165.31 |
| **d** | 1625 | 5.33 | 56.18 | 169.46 |
| **e** | 1630 | 5.40 | – | – |
| **f** | 1630 | 5.30 | 55.92 | 172.18 |
| **g** | 1630 | 5.33 | 58.51 | 170.49 |

nitrile **2** (0.1 mol) are placed in a 500 ml flask equipped with a cooler. At a temperature of 80 °C, a suspension of paraformaldehyde (**1**; 4.5 g, 0.05 mol) in chlorobenzene (20 ml) is gradually added with shaking and the mixture is shaken at 80 °C for the time listed in Table 1. The resin is then filtered off (it does not show any loss of activity and can be used again), the solvent is evaporated, and the solid residue is recrystallized from toluene.

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